Retina 2018
The Art + Science of Retina + Vitreous

Program Directors
Richard F Spaide MD and Mark S Humayan MD PhD

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

McCormick Place
Chicago, Illinois
Friday-Saturday, Oct. 26-27, 2018

Presented by:
The American Academy of Ophthalmology

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2018 Retina Subspecialty Day Planning Group

On behalf of the American Academy of Ophthalmology and the American Society of Retina Specialists, the Macula Society, the Retina Society, and Club Jules Gonin, it is our pleasure to welcome you to Chicago and **Retina 2018: The Art + Science of Retina + Vitreous.**

Richard F Spaide MD
Program Director

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Mark S Humayun MD PhD
Program Director

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National Eye Institute: S
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Ocular Therapeutix Inc.: C
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Thieme Medical Publishers: C
U.S. Food and Drug Administration: C,S

AAO Staff

Ann L'Estrange
None

Carolyn Little
None

Melanie Rafaty
None

Debra Rosencrance
None

Beth Wilson
None

Retina 2018 Contents

The Charles L Schepens MD Lecture

Developing Therapies for AMD: The Art and Science of Problem Solving

Friday, Oct. 26, 2018
9:24 AM – 9:44 AM

Joan W Miller MD

Joan W Miller MD is the David Glendenning Cogan Professor of Ophthalmology and chair of the Department of Ophthalmology at Harvard Medical School, and chief of ophthalmology at Massachusetts Eye and Ear and Massachusetts General Hospital. Dr. Miller earned her medical degree and received her ophthalmology residency training from Harvard Medical School, and then completed fellowships in ophthalmology research and vitreoretinal surgery at Mass. Eye and Ear. In 2003, Dr. Miller became the first female physician to achieve the rank of professor of ophthalmology at Harvard Medical School, and the first woman to serve as chair of the Department of Ophthalmology. She is also the first woman appointed as chief of ophthalmology at both Mass. Eye and Ear and Massachusetts General Hospital.

Dr. Miller is an internationally recognized expert on retinal disorders, including AMD. Over the last two decades, she and her colleagues at Mass. Eye and Ear / Harvard Medical School pioneered the development of photodynamic therapy using verteporfin (Visudyne), the first approved pharmacological therapy able to reduce and slow vision loss in patients with AMD. The group also identified the key role of vascular endothelial growth factor (VEGF) in ocular neovascularization, leading to the development of anti-VEGF therapies now administered to millions of children and adults with sight-threatening retinal diseases annually around the world. Dr. Miller's current studies focus on the genetics of AMD, strategies for early intervention in AMD, and neuroprotective therapies for retinal diseases.

Dr. Miller has authored more than 200 original research articles and nearly 80 book chapters, review articles, or editorials. She is on the editorial board for the journals *Ophthalmology* and *Ophthalmology Retina* and is an editor of several textbooks, including the third edition of Albert and Jakobiec's *Principles and Practice of Ophthalmology* (Saunders). Dr. Miller is a member of the National Academy of Medicine, the Academia Ophthalmologica Internationalis, and the Dowling Society, as well as a Gold Fellow of Association for Research in Vision and Ophthalmology (ARVO). Among her numerous honors, Dr. Miller delivered the 2012 Edward Jackson Lecture for the American Academy of Ophthalmology and was a corecipient of the 2014 António Champalimaud Vision Award, the highest distinction in ophthalmology and visual science. In 2015, Dr. Miller became the first woman to receive the Mildred Weisenfeld Award for Excellence in Ophthalmology from ARVO. Recently, Dr. Miller was named the 2018 recipient of the celebrated Lucien Howe Medal from the American Ophthalmological Society for her distinguished service to the fields of retina and ophthalmology.

CME Credit

Academy's CME Mission Statement

The purpose of the American Academy of Ophthalmology's Continuing Medical Education (CME) program is to present ophthalmologists with the highest quality lifelong learning opportunities that promote improvement in physician practices, resulting in the best possible eye care for their patients.

2018 Retina Subspecialty Day Learning Objectives

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

- Present established and innovative approaches to the management of surgical and retinal vascular conditions
- 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, pediatric retinal diseases, 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

2018 Retina Subspecialty Day 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.

2018 Retina Subspecialty Day CME Credit

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

The American Academy of Ophthalmology designates this live activity for a maximum of 14 *AMA PRA Category 1 Credits*™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

Teaching at a Live Activity

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

Scientific Integrity and Disclosure of 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.

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

Control of Content

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

Attendance Verification for CME Reporting

Before processing your requests for CME credit, the American Academy of Ophthalmology must verify your attendance at Subspecialty Day and/or AAO 2018. In order to be verified for CME or auditing purposes, you must either:

- Register in advance, receive materials in the mail, and turn in the *Subspecialty Day Syllabi* exchange voucher(s) onsite;
- Register in advance and pick up your badge onsite if materials did not arrive before you traveled to the meeting;
- Register onsite; or
- Scan the barcode on your badge as you enter an AAO 2018 course or session room.

CME Credit Reporting

South Building Level 2.5 and Academy Resource Center

Attendees whose attendance has been verified (see above) at AAO 2018 can claim their CME credit online during the meeting. Registrants will receive an email during the meeting with the link and instructions on how to claim credit.

Onsite, you may report credits earned during Subspecialty Day and/or AAO 2018 at the CME Credit Reporting booth.

Academy Members

The CME credit reporting receipt is not a CME transcript. CME transcripts that include AAO 2018 credits entered at the Academy's annual meeting will be available to Academy members through the Academy's CME web page (www.aao.org/cme-central) beginning Thursday, Dec. 13.

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 2018.

Nonmembers

The Academy provides nonmembers with verification of credits earned and reported for a single Academy-sponsored CME activity. To obtain a printed record of your credits, claim CME credits onsite at the CME Credit Reporting kiosks. Nonmembers choosing to claim online through the Academy's CME web page (www.aao.org/cme-central) after December 13 will have one opportunity to print a certificate.

Proof of Attendance

The following types of attendance verification are available during AAO 2018 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, Level 2.5, and in the Academy Resource Center.

Faculty

David H Abramson MD FACS
New York, NY

Lloyd P Aiello MD PhD
Boston, MA

Jorge G Arroyo MD
Brookline, MA

Nisha Acharya MD
San Francisco, CA

Rajendra S Apte MD PhD
Saint Louis, MO

Robert L Avery MD
Santa Barbara, CA

Anita Agarwal MD
San Francisco, CA

J Fernando Arevalo MD FACS
Baltimore, MD

Carl C Awh MD
Nashville, TN

Sophie J Bakri MD
Rochester, MN

Caroline R Baumal MD
Boston, MA

Susanne Binder MD
Vienna, Austria

Alay S Banker MD
Ahmedabad, India

Audina M Berrocal MD
Miami, FL

Barbara Ann Blodi MD
Madison, WI

No photo available

Irene A Barbazetto MD
New York, NY

Maria H Berrocal MD
San Juan, PR

David S Boyer MD
Los Angeles, CA

Charles C Barr MD FACS
Louisville, KY

Cagri G Besirli MD
Ann Arbor, MI

Neil M Bressler MD
Baltimore, MD

Susan B Bressler MD
Baltimore, MD

Antonio Capone Jr MD
Royal Oak, MI

Andrew A Chang FRANZCO PhD
Sydney, Australia

David M Brown MD
Houston, TX

Colleen M Cebulla MD PhD
Columbus, OH

Steven T Charles MD
Germantown, TN

David J Browning MD PhD
Charlotte, NC

Usha Chakravarthy MBBS PhD
Belfast, Northern Ireland

Gemmy Chui Ming Cheung MB BChir FRCOphth
Singapore, Singapore

Alexander J Brucker MD
Philadelphia, PA

R V Paul Chan MD
Chicago, IL

Emily Y Chew MD
Bethesda, MD

Jay K Chhablani MBBS
Hyderabad, India

Karl G Csaky MD
Dallas, TX

Diana V Do MD
Los Altos, CA

David R Chow MD
North York, ON, Canada

No photo available

Catherine A Cukras MD PhD
Bethesda, MD

Kimberly A Drenser MD PhD
Royal Oak, MI

Carl C Claes MD
Schilde, Belgium

Emmett T Cunningham Jr MD PhD MPH
Hillsborough, CA

Pravin U Dugel MD
Phoenix, AZ

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Jason I Comander MD PhD
Boston, MA

Janet Louise Davis MD
Miami, FL

Jay S Duker MD
Boston, MA

Claus Eckardt MD
Frankfurt, Germany

Amani Fawzi MD
Chicago, IL

James C Folk MD
Iowa City, IA

No photo available

Ehab N El Rayes MD PhD
Cairo, Egypt

Philip J Ferrone MD
Great Neck, NY

William R Freeman MD
La Jolla, CA

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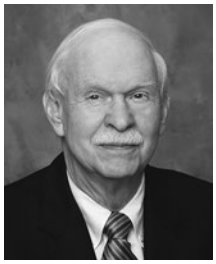
Dean Eliott MD
Boston, MA

Yale L Fisher MD
New York, NY

K Bailey Freund MD
New York, NY

Nicole Eter MD
Muenster, Germany



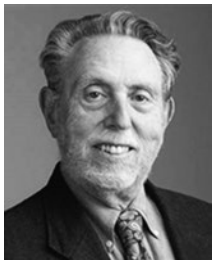
Harry W Flynn Jr MD
Miami, FL

Mark C Gillies MD PhD
Sydney, NSW, Australia

Giampaolo Gini MD
Florence, Italy

M Gilbert Grand MD
Saint Louis, MO

Dennis P Han MD
Milwaukee, WI



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La Jolla, CA

Jeffrey G Gross MD
Columbia, SC

Mary Elizabeth Hartnett MD FACS
Salt Lake City, UT

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Andrew V Gomes MD
São Paulo, Brazil

No photo available

Robyn H Guymer MBBS PhD
East Melbourne, Australia

Sohail J Hasan MD PhD
Orland Park, IL

Evangelos S Gragoudas MD
Boston, MA

Julia A Haller MD
Philadelphia, PA

Tarek S Hassan MD
Royal Oak, MI

Jeffrey S Heier MD
Boston, MA

Mark S Humayun MD PhD
Los Angeles, CA

Mark W Johnson MD
Ann Arbor, MI

Allen C Ho MD
Philadelphia, PA

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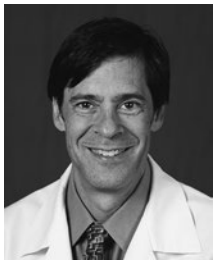
Gustavo Matias Huning MD
Porto Alegre, Brazil

Kazuaki Kadonosono MD
Yokohama, Kanagawa, Japan

Frank G Holz MD
Bonn, Germany



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Durham, NC

Peter K Kaiser MD
Cleveland, OH

G Baker Hubbard MD
Atlanta, GA

Lee M Jampol MD
Chicago, IL

Amir H Kashani MD PhD
Pasadena, CA

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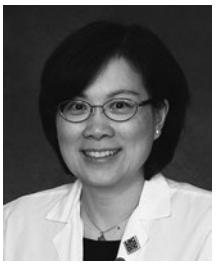
Arshad M Khanani MD
Reno, NV

John W Kitchens MD
Lexington, KY



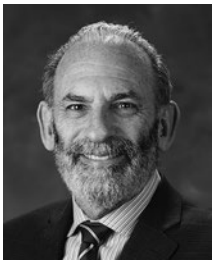
Jennifer Irene Lim MD
Chicago, IL

Rahul Khurana MD
Mountain View, CA

Frank H Koch MD
Frankfurt, Germany

Anat Loewenstein MD
Tel Aviv, Israel

Judy E Kim MD
Milwaukee, WI



Baruch D Kuppermann MD PhD
Irvine, CA

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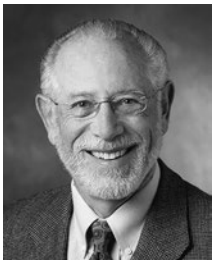
Brandon J Lujan MD
Portland, OR

Szilard Kiss MD
New York, NY

Geeta A Lalchandani-Lalwani MD
Boulder, CO



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Palo Alto, CA

Daniel F Martin MD
Cleveland, OH

William F Mieler MD
Winnetka, IL

Timothy B Murray MD MBA
South Miami, FL

Carlos Mateo MD
Barcelona, Spain

Joan W Miller MD
Boston, MA

No photo available

Priya Narang MS
Ahmedabad, India

Colin A McCannel MD
Los Angeles, CA

No photo available

Yuki Morizane MD
Okayama, Japan

Quan Dong Nguyen MD
Palo Alto, CA

Tara A McCannel MD
Los Angeles, CA

Prithvi Mruthyunjaya MD
Palo Alto, CA

Masahito Ohji MD
Otsu, Shiga, Japan

Kyoko Ohno-Matsui MD
Tokyo, Japan

Barbara Parolini MD
Brescia, BS, Italy

Jonathan L Prenner MD
Princeton, NJ

Andrew J Packer MD
Manchester, CT

Grazia Pertile MD
Negrar, Italy

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Jose S Pulido MD MS
Rochester, MN

Kirk H Packo MD
Chicago, IL

Dante Pieramici MD
Santa Barbara, CA

Hugo Quiroz-Mercado MD
Mexico City, Mexico

David W Parke II MD
San Francisco, CA

John S Pollack MD
Joliet, IL

Narsing A Rao MD
Los Angeles, CA

Carl D Regillo MD FACS
Bryn Mawr, PA

Stanislao Rizzo MD
Lucca, Italy

Srinivas R Sadda MD
Los Angeles, CA

No photo available

Elias Reichel MD
Boston, MA

Richard B Rosen MD
New York, NY

Jose A Sahel MD
Pittsburgh, PA

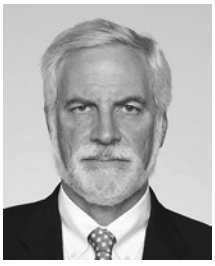
Kourous Rezaei MD
Harvey, IL

Philip J Rosenfeld MD PhD
Miami, FL

David Sarraf MD
Los Angeles, CA

William L Rich III MD FACS
Lusby, MD

Edwin Hurlbut Ryan Jr MD
Edina, MN



Andrew P Schachat MD
Cleveland, OH

Amy C Schefler MD
Houston, TX

Hatice N Sen MD
Bethesda, MD

Lawrence J Singerman MD
Beachwood, OH

Ursula M Schmidt-Erfurth MD
Vienna, Austria

Chirag P Shah MD MPH
Boston, MA

Rishi P Singh MD
Cleveland, OH

Adrienne Williams Scott MD
Baltimore, MD

Gaurav K Shah MD
Town and Country, MO

Jason S Slakter MD
New York, NY

Ingrid U Scott MD MPH
Hershey, PA

Michael A Singer MD
San Antonio, TX

Elliott H Sohn MD
Iowa City, IA

Richard F Spaide MD
New York, NY

Paul Sternberg Jr MD
Nashville, TN

Hiroko Terasaki MD
Nagoya, Japan

Sunil K Srivastava MD
Cleveland, OH

Edwin M Stone MD PhD
Iowa City, IA

No photo available

Asheesh Tewari MD
Dearborn, MI

Paulo E Stanga MD
Nether Alderley, Cheshire, England

Jennifer K Sun MD
Boston, MA

John T Thompson MD
Baltimore, MD

Giovanni Staurenghi MD
Milan, Italy

Ramin Tadayoni MD PhD
Paris, France

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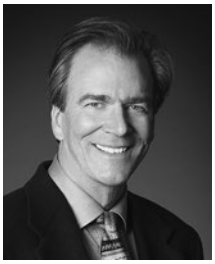
Daniele Tognetto MD
Catania, Italy

Paul E Tornambe MD
Poway, CA



Albert T Vitale MD
Salt Lake City, UT

John A Wells III MD
West Columbia, SC

Cynthia A Toth MD
Durham, NC

No photo available

Alan L Wagner MD FACS
Norfolk, VA

George A Williams MD
Royal Oak, MI

Michael T Trese MD
Royal Oak, MI

Nadia Khalida Waheed MD
Cambridge, MA

David J Wilson MD
Portland, OR

Russell N Van Gelder MD PhD
Seattle, WA

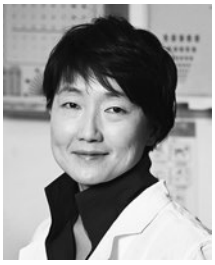
No photo available

Dale Webster PhD
Mountain View, CA

Sebastian Wolf MD PhD
Bern, Switzerland

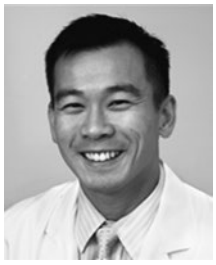
Tien Yin Wong MBBS
Singapore, Singapore

Lawrence A Yannuzzi MD
New York, NY



Seung Young Yu MD PhD
Seoul, Korea

Lihteh Wu MD
San Jose, Costa Rica



Steven Yeh MD
Atlanta, GA

No photo available

David N Zacks MD PhD
Ann Arbor, MI

Charles C Wykoff MD PhD
Houston, TX

No photo available

Young Hee Yoon MD
Seoul, Korea

Marco A Zarbin MD PhD FACS
Chatham, NJ

Retina 2018: The Art + Science of Retina + Vitreous

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

FRIDAY, OCT. 26

7:00 AM	Continental Breakfast		
8:00 AM	Welcome and Introductions	Richard F Spaide MD* Mark S Humayun MD PhD*	

Section I: The Art of Vitreoretinal Surgery

Moderators: John S Pollack MD* and David N Zacks MD PhD*

8:05 AM	Treatment of Persistent Hypotony in Eyes With Successfully Treated Proliferative Vitreoretinopathy	Tarek S Hassan MD*	1
8:10 AM	Butterfly Sutures for Temporary Closure of Sclerotomies	Claus Eckardt MD	3
8:15 AM	Top 3 Avoidable Problems Leading to Redetachment	Steven T Charles MD*	4
8:20 AM	Pearls for Large Macular Holes	Carl C Claes MD*	6
8:25 AM	Tips for Myopic Eyes	Hiroko Terasaki MD*	7

Section II: Vitreoretinal Surgery, Part I

Moderators: Maria H Berrocal MD* and John W Kitchens MD*

8:30 AM	A New Way to Close Holes and Breaks	Stanislao Rizzo MD	11
8:37 AM	Hypersonic Vitrectomy: Continued Clinical Experience and Technical Improvements	Carl C Awh MD*	12
8:44 AM	Development of a Deep Learning System for Digitally Enhanced Internal Limiting Membrane Peeling	Kazuaki Kadonosono MD	13
8:51 AM	Final Visual Acuity, Not Amount of Improvement, Must Be the Measure of Our Success in Epiretinal Membrane Surgery	Colin A McCannel MD*	14
8:58 AM	Management of Complications Correlated With the Use of Intraocular Tamponade	Grazia Pertile MD	15
9:05 AM	Vitrectomy for Diabetic Macular Edema: Why, How, and When	Gaurav K Shah MD*	16
9:12 AM	Myopic Foveoschisis	Ramin Tadayoni MD PhD*	17

The Charles L Schepens MD Lecture

9:19 AM	Introduction of the 2018 Charles L Schepens MD Lecture	David W Parke II MD*	
9:24 AM	Developing Therapies for AMD: The Art and Science of Problem Solving	Joan W Miller MD*	19
9:44 AM	REFRESHMENT BREAK and RETINA EXHIBITS		

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

Section III: The Business of Retina

Moderator: Geeta A Lalwani MD*

10:29 AM	Advocating for the Profession and Patients	Sohail J Hasan MD PhD	21
10:34 AM	Retinal Malpractice Issues: The 30-Year OMIC Experience	George A Williams MD*	24
10:41 AM	MACRA and Beyond	William L Rich III MD FACS	25
10:48 AM	Efficient Workflow	Dennis P Han MD*	26

Section IV: My Best Medical Retina Cases

Moderator: William F Mieler MD

10:55 AM	Case Presentation	David Sarraf MD*	28
10:58 AM	Discussion		
11:01 AM	Case Presentation	K Bailey Freund MD*	29
11:04 AM	Discussion		
11:07 AM	Case Presentation	Lee M Jampol MD	30
11:10 AM	Discussion		
11:13 AM	Case Presentation	Anita Agarwal MD	31
11:16 AM	Discussion		
11:19 AM	Case Presentation	William F Mieler MD	32
11:22 AM	Discussion		

Section V: Medical Retina, Part I

Moderator: Paul Sternberg Jr MD*

11:25 AM	Port Delivery Phase 2 LADDER AMD Study Results	Carl D Regillo MD FACS*	33
11:32 AM	Subthreshold Laser Therapies for Diabetic Macular Edema: A Review of All Subthreshold Laser Technologies Available to Treat DME	Elias Reichel MD*	34
11:39 AM	Micropulse Laser vs. Photodynamic Therapy for Central Serous Chorioretinopathy	Jay K Chhablani MBBS	35
11:46 AM	Time-Elapsed Studies of the Retinal Capillaries in Clinical Vascular Disease Using Adaptive Optics: What Do They Tell Us?	Richard B Rosen MD*	37
11:53 AM	Optic Nerve Damage Due to Increased IOP Secondary to Dexamethasone Implant	Michael A Singer MD*	42

Section VI: Special Lecture

Moderator: Richard F Spaide MD*

12:00 PM	Machine Interpretation of Fundus Photographs	Dale Webster PhD*	43
12:12 PM	LUNCH and RETINA EXHIBITS		

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

Section VII: Uveitis

Moderator: Daniel F Martin MD

1:37 PM	Vitrectomy and Uveitis	Janet Louise Davis MD*	44
1:44 PM	Drug-Induced Uveitis	Emmett T Cunningham Jr MD PhD MPH	45
1:51 PM	Polymerase Chain Reaction	Russell N Van Gelder MD PhD*	47
1:58 PM	Three Pearls for Uveitis	Narsing A Rao MD	48
2:05 PM	Uveitis Case Panel Discussion		49
	Panel Moderator: Sunil K Srivastava MD*		
	Panelists: Nisha Acharya MD*, Hatice N Sen MD, Albert T Vitale MD*, Steven Yeh MD*		

Section VIII: My Coolest Surgical Video

Moderator: Masahito Ohji MD*

Panelists: Jorge G Arroyo MD, Sophie J Bakri MD*, Susanne Binder MD*, Allen C Ho MD*, Edwin Hurlbut Ryan Jr MD*

2:25 PM	Internal Limiting Membrane Repositioning for Macular Hole Due to Rupture of Retinal Macroaneurysm	Yuki Morizane MD	50
2:27 PM	Discussion		
2:30 PM	Surgical Pupilloplasty for Secondary Angle Closure Glaucoma Induced by Silicone Oil Tamponade	Priya Narang MS	50
2:32 PM	Discussion		
2:35 PM	Use of Intraoperative OCT in Ensuring Optimal Array-Retina Contact During Argus II Implantation Surgery	Young Hee Yoon MD*	50
2:37 PM	Discussion		
2:40 PM	What to Do When Your Fluid/Air Exchange Doesn't Work?	Gustavo Matias Huning MD	50
2:42 PM	Discussion		
2:45 PM	Foldable Suretinal Scaffold With Stem Cell Derived RPE in GA	Amir H Kashani MD PhD*	50
2:47 PM	Discussion		
2:50 PM	Audience Vote		

Section IX: Pediatric Retina

Moderator: R V Paul Chan MD*

2:52 PM	Anti-VEGF for ROP: What Drug and What Dose?	Robert L Avery MD*	51
2:59 PM	Clinical Features and Management of "Crunch" Detachments Following Anti-VEGF Treatment for ROP	Antonio Capone Jr MD*	52
3:06 PM	Repair and Regeneration Wnt Signaling: What and Why	Michael T Trese MD*	53
3:13 PM	Anti-VEGF Treatment for ROP: Clinical Trials and Phenotypic Differences Worldwide	Mary Elizabeth Hartnett MD FACS*	54
3:20 PM	Pediatric Retina Panel		56
	Panel Moderator: Philip J Ferrone MD*		
	Panelists: Audina M Berrocal MD*, Cagri G Besirli MD*, Kimberly A Drenser MD PhD*, G Baker Hubbard MD		
	REFRESHMENT BREAK with the EXPERTS and RETINA EXHIBITS		

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BREAK with the EXPERTS, Hall E

Moderators: M Gilbert Grand MD and Andrew J Packer MD

3:35 PM	AMD, Dry	Marco A Zarbin MD PhD FACS
	AMD, Wet	David M Brown MD Jeffrey S Heier MD
	Business of Retina	Richard A Garfinkel MD William L Rich III MD FACS Reginald J Sanders MD
	Diabetic Retinopathy	Susan B Bressler MD Jennifer K Sun MD
	Gene Therapy	Mark E Pennesi MD PhD
	Intraocular Tumors	Timothy G Murray MD MBA
	Machine Learning and Artificial Intelligence	Aaron Y Lee MD
	Macular Holes	John T Thompson MD
	New Instrumentation	David R Chow MD
	OCT Angiography	Caroline R Baumal MD
	Ocular Imaging	Amani Fawzi MD David Sarraf MD
	Pediatric Retinal Disease	Audina M Berrocal MD Philip J Ferrone MD
	Retinal Detachment	Gary W Abrams MD J Michael Jumper MD Hiroko Terasaki MD
	Vascular Occlusions	Michael S Ip MD Ingrid U Scott MD MPH

Section X: Late Breaking Developments, Part I

Moderator: Mark S Humayun MD PhD*

Panelists: David S Boyer MD*, Alexander J Brucker MD*, Baruch D Kuppermann MD PhD*

4:20 PM	Relentless Long-term Progression of Hydroxychloroquine Retinopathy	Michael F Marmor MD	57
4:25 PM	Panel Discussion		
4:28 PM	Visual Function after Anti-VEGF Therapy for Macular Edema due to Central Retinal Vein Occlusion: SCORE2 Trial Results	Ingrid U Scott MD MPH	57
4:33 PM	Panel Discussion		
4:36 PM	24-month Evaluation of Fluocinolone Acetonide Intravitreal Insert Treatment for Non-Infectious Posterior Uveitis	Quan Dong Nguyen MD	57
4:41 PM	Panel Discussion		
4:44 PM	Sub-Threshold Nanosecond Laser Intervention in Age-Related Macular Degeneration: The LEAD Randomized Controlled Clinical Trial	Robyn H Guymer MBBS PhD	57
4:49 PM	Panel Discussion		
4:52 PM	First Results of Photovoltaic Vision Restauration in Atrophic Dry Age-related Macular Degeneration	Jose A Sahel MD	57
4:57 PM	Panel Discussion		

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5:00 PM	New Low-cost Intravitreal Biosimilars (Bevacizumab and Ranibizumab) for Retinal Vascular Diseases	Alay S Banker MD	57
5:05 PM	Panel Discussion		

Section XI: First-time Results of Clinical Trials

Moderator: Julia A Haller MD*

5:08 PM	26 Week Results of the Phase I Study to Evaluate Safety & Tolerability of RGX-314 Gene Therapy in nAMD Subjects	Jeffrey S Heier MD	58
5:15 PM	Safety and Efficacy of Abicipar in Patients with Neovascular Age-related Macular Degeneration	Rahul Khurana MD	58
5:22 PM	Simultaneous Inhibition of VEGF and Ang-2 with Faricimab in Neovascular AMD: STAIRWAY Phase 2 Results	Arshad M Khanani MD	58
5:29 PM	Brimonidine DDS Safety and Efficacy in Patients with Geographic Atrophy Secondary to Age-related Macular Degeneration	William R Freeman MD	58
5:36 PM	Closing Remarks	Mark S Humayun MD PhD Richard F Spaide MD	

SATURDAY, OCT. 27

7:00 AM	Continental Breakfast		
8:00 AM	Opening Remarks	Mark S Humayun MD PhD Richard F Spaide MD	

Section XII: Imaging

Moderators: Brandon J Lujan MD* and Amani Fawzi MD

8:05 AM	Clinical Utility of OCT Angiography	Jay S Duker MD*	59
8:12 AM	Are OCT Angiographic Images the Same Among Different Devices?	Giovanni Staurenghi MD*	64
8:19 AM	Sickle Cell Retinopathy: New Findings From OCT/ OCT Angiography	Jennifer Irene Lim MD*	66
8:26 AM	OCT Angiography Smash Hits	Nadia Khalida Waheed MD*	68
8:33 AM	Imaging the Neurovascular Unit	Richard F Spaide MD*	69
8:40 AM	New Modes of Autofluorescence Imaging	Frank G Holz MD*	70
8:47 AM	Multimodal Pediatric Retinal Imaging for Vitreoretinal Surgical Planning	Cynthia A Toth MD*	73
8:54 AM	Swept-Source OCT and OCT Angiography for Pathologic Myopia	Kyoko Ohno-Matsui MD	74
9:01 AM	Hyper-reflective Foci: A Relevant Biomarker for Macular Disease Activity	Ursula M Schmidt-Erfurth MD*	76

Section XIII: Late Breaking Developments, Part II

Moderator: Hugo Quiroz-Mercado MD*

9:08 AM	Phase 3, Randomized, Double-Masked, Multicenter Trials of Brolucizumab vs. Aflibercept for Neovascular AMD: Ninety-Six-Week Results From the HAWK and HARRIER Studies	Pravin U Dugel MD	79
9:13 AM	Use of Intravitreal Aflibercept Treat-and-extend Dosing for Wet Age-related Macular Degeneration: 96-week ALTAIR Results	Masahito Ohji MD	80
9:18 AM	Identifying Ophthalmological Diagnoses and Treatable Diseases by Image-Based Deep Learning	Michael Goldbaum MD MS	80

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Section XIV: Neovascular AMD

Moderator: Irene A Barbazetto MD*

Section XV: Oncology Panel

Panel Moderator: Prithvi Mruthyunjaya MD*

Panelists: David H Abramson MD FACS, Colleen M Cebulla MD PhD*, Evangelos S Gragoudas MD*, Tara A McCannel MD, Timothy G Murray MD MBA, Amy C Schefler MD*

Section XVI: Diabetes

Moderators: Lloyd P Aiello MD PhD* and Lawrence J Singerman MD*

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12:09 PM	Diabetes Panel Discussion Panel Moderator: Judy E Kim MD* Panelists: J Fernando Arevalo MD FACS*, Barbara Ann Blodi MD, Diana V Do MD*, Rishi P Singh MD*, Jennifer K Sun MD*		107
12:24 PM	LUNCH and AAO 2018 EXHIBITS		

Section XVII: Innovative Retinal Interventions

Moderators: Yale L Fisher MD and Rajendra S Apte MD PhD*

1:39 PM	Nano-retina	Marco A Zarbin MD PhD FACS*	108
1:46 PM	Gene Therapy	Szilard Kiss MD*	110
1:53 PM	An Injectable Fluocinolone Implant for Posterior Uveitis: One-Year Results From Two Phase 3 Clinical Trials	Glenn J Jaffe MD*	114
2:00 PM	TIE2 Activation in the Management of Diabetic Retinopathy and Diabetic Macular Edema	Peter K Kaiser MD*	115
2:07 PM	Combined Blockade of Angiopoeitin-2 and VEGF-A With RG7716 in Phase 2 Diabetic Macular Edema and Neovascular AMD Trials: What's New and What's to Come	Charles C Wykoff MD PhD*	117
2:14 PM	The Art and Science of YAG Vitreolysis	Chirag P Shah MD MPH*	120

Section XVIII: Non-neovascular AMD

Moderators: Caroline R Baumal MD* and Catherine A Cukras MD PhD

2:21 PM	Apl-2 Treatment for Geographic Atrophy: Long-term Results	David S Boyer MD*	121
2:28 AM	A Simple OCT-Based System for Staging Dry AMD	Srinivas R Sadda MD*	122
2:35 PM	The Natural History of Geographic Atrophy in AREDS2	Emily Y Chew MD	125
2:42 PM	Does the OCT Double Layer Sign in Nonexudative Macular Diseases Indicate Subclinical Neovascularization?	Philip J Rosenfeld MD PhD*	126
2:49 PM	Cuticular Drusen: Risk Factors for Advanced AMD	Lawrence A Yannuzzi MD	129

Section XIX: Vitreoretinal Surgery, Part II

Moderators: Charles C Barr MD FACS and Jonathan L Prenner MD*

2:56 PM	Endophthalmitis and Pseudoendophthalmitis Following Intravitreal Injections	Harry W Flynn Jr MD	130
3:03 PM	Anterior Segment Complications of Multiple Intravitreal Injections	John T Thompson MD*	132
3:10 PM	New Instrumentation	David R Chow MD*	134
3:17 PM	Case Studies and Management Panel Panel Moderator: Dean Eliott MD* Panelists: Giampaolo Gini MD, Carlos Mateo MD*, Kirk H Packo MD*, Adrienne Williams Scott MD*, Paulo E Stanga MD*, Paul E Tornambe MD*		135
3:37 PM	REFRESHMENT BREAK and AAO 2018 EXHIBITS		

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Section XX: Medical Retina, Part II

Moderator: Jason S Slakter MD*

4:14 PM	Analysis of the Intestinal Microbiome in Retinal Diseases	Sebastian Wolf MD PhD*	136
4:21 PM	New Concepts in Classifying Myopic Macular Degeneration	Tien Yin Wong MBBS*	137
4:28 PM	Affordable Stem Cell Therapies	Edwin M Stone MD PhD	139
4:35 PM	ZEBRA Study Executive Summary	Alan L Wagner MD FACS*	140
4:38 PM	Medical Retina Panel Discussion Panel Moderator: Jose S Pulido MD MS* Panelists: Usha Chakravarthy MBBS PhD*, Jay K Chhablani MBBS, Karl G Csaky MD*, James C Folk MD*, Lihteh Wu MD*, Seung Young Yu MD PhD*		141

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

Moderator: Kourous Rezaei MD*

Panelists: Andrew Chang MD, Ehab N El Rayes, MD PHD, Andre V Gomes MD, Frank H Koch MD, Barbara Parolini MD, Elliott H Sohn MD*, Asheesh Tewari MD, Daniele Tognetto MD

4:58 PM	Silicone Oil	Asheesh Tewari MD	142
5:01 PM	Discussion		
5:04 PM	Retinal Detachment Surgery	Andrew A Chang FRANZCO PhD	142
5:07 PM	Discussion		
5:10 PM	Perfluoron	Andre V Gomes MD	142
5:13 PM	Discussion		
5:16 PM	Anesthesia	Daniele Tognetto MD	142
5:19 PM	Discussion		
5:22 PM	Macular Surgery	Ehab N El Rayes, MD PhD	142
5:25 PM	Discussion		
5:28 PM	Closing Remarks	Richard F Spaide MD* Mark S Humayun MD PhD*	

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Treatment of Persistent Hypotony in Successfully Treated Proliferative Vitreoretinopathy

Tarek S Hassan MD

I. Hypotony in Eyes With Attached Retinas After PVR Repair: Major Causes
   A. Ciliary body abnormalities
      1. Anterior fibrous proliferation/PVR
      2. Ischemia
      3. Trauma
   B. Choroidal detachment
   C. Surgical or traumatic filtering bleb
   D. Uveoscleral outflow abnormalities

II. Uveoscleral Outflow: The Alternative Pathway

   Fluid passes through suprachoroidal space, ciliary muscle, choroidal vessels, emissarial canals, sclera, lymphatics.

   A. Aqueous removed through, around, and between tissues.
   B. Pressure independent for the most part
   C. Responsible for 5%-35% of aqueous outflow
   D. If excessive, can lead to hypotony
      1. Decreased with miotics
      2. Decreased with ciliary body contraction
      3. Increased with ciliary body relaxation
   E. Increased by large retinectomies … leads to more hypotony
      1. Higher incidence with larger retinectomies; more bare retinal pigment epithelium and sclera
      2. Results in post–retinal detachment / PVR repair hypotony in 15%-40% of eyes
      3. Lower incidence in eyes with silicone oil

III. Long-term Effects of Chronic Hypotony
   A. Macular edema
   B. Choroidal folds
   C. Optic nerve edema
   D. Uveal edema
   E. Reduced vision
   F. Ultimately … phthisis

IV. Ways to Raise IOP
   A. Ibopamine: Sympathomimetic prodrug of epinine; dopamine 1 receptor agonist
      1. Increased aqueous production leads to increased IOP.
      2. Severe ocular irritation limited completion of trials and clinical usage.
   B. Viscoelastic in the anterior chamber
   C. Viscoelastic in the vitreous cavity
   D. Fluid–gas exchange
   E. Silicone oil
   F. Steroids: Increase IOP by 25%-75%
      1. Topical
         a. Difluprednate > dexamethasone, prednisolone > fluoromethalone, hydrocortisone, rimexolone
         b. 25%-30% increase in IOP
      2. Periocular: triamcinolone (40 mg), 25%-50% > 5 mmHg ↑ IOP
      3. Intravitreal
         a. Triamcinolone: 20%-50% > 5 mmHg ↑ IOP
         b. Dexamethasone implant: 25+% > 10 mmHg ↑ IOP
         c. Fluocinolone implant: 75% needed IOP-lowering meds; 36% needed incisional surgery

V. Steroid Treatment of Post-PVR Repair Hypotony: Our Series (Associated Retinal Consultants; Royal Oak, Michigan)
   A. 11 consecutive eyes / 11 patients (IOP < 5 for at least three months after last surgery)
      1. Retrospective review: > 3 months follow-up
      2. All eyes with completely attached retinas after PVR repair(s)
      3. Exclusion: No anterior PVR on ciliary body or angle, choroidal detachment, clefts, filtering blebs, or active uveitis
   B. Intervention: Steroids – topical ± intravitreal
      1. All eyes previously on long-term prednisolone drops q.i.d.
      2. Difluprednate q.i.d. given to 11/11 eyes
         a. 5/11: additional dexamethasone implant
         b. 2/11: additional intravitreal triamcinolone injection

C. Results

1. IOP: Mean IOP ↑ from 4.0 to 11.0 among all eyes ($P < .001$)
    a. Effect of difluprednate: Mean IOP ↑ from 4.2 to 10.7 among eyes that only received difluprednate ($P < 00.1$)
    b. No significant additive effect from intravitreal triamcinolone or dexamethasone implant
    c. Effect seen gradually over several months
2. VA: No significant change
3. No statistically significant difference between:
    a. Pseudophakic and aphakic eyes
    b. Eyes with silicone oil still in place and those without
4. Study limitations
    a. Small uncontrolled retrospective series
    b. Office IOP measurements (done consistently)
    c. Variable pre-steroid treatment PVR courses
    d. Unknown history of undiagnosed glaucoma prior to PVR

VI. IOP Rise Following Steroids

A. Anatomic changes within and between trabecular meshwork cells

1. Increased deposition of actin and myocilin; mutations in myocilin gene may determine IOP response.
2. Increased fibronectin, GAGs, and elastin
3. Upregulation of glucocorticoid receptors

B. Difluprednate

1. Rapidly penetrates corneal epithelium and then deacetylates into its active form
2. 6x more powerful than prednisolone
3. Unpredictable and dramatic IOP elevations have been reported; increased IOP in post-vitrectomy eyes vs. prednisolone.

VII. Conclusions

A. End-state persistent hypotony in some eyes successfully treated for PVR retinal detachments can be treatable with aggressive topical difluprednate.

1. Assume these are eyes with ciliary body ischemia and/or increased uveoscleral outflow
2. Unknown if effect lasts indefinitely
3. Unknown if any long-term anatomic changes allow for reduction or stopping treatment at some point
4. Prospective controlled trials in progress

B. Other drugs or combinations may be of benefit in the future.

Selected Readings

1. Fine HF, Biscette O, Chang S, Schiff WM. Ocular hypotony: a review. *Comp Ophthalmol Update*. 2007; 8:29-37.
2. Kunimoto DY, Kenitkar KD, Makar M. Hypotony. In: *The Will's Eye Manual*. Lippincott, Williams, & Wilkins; 2004:440-442.
3. O'Connell SR, Majji AB, Humayun MS, de Juan E Jr. The surgical management of hypotony. *Ophthalmology* 2000; 107(2):318-323.
4. Stead RE, Juma Z, Turner S, Jones LD, Sung VC. A novel use of reticulated hyaluronic acid (Healaflow) for hypotony eyes in patients with uveitis. *Br J Ophthalmol*. 2016 Mar 25.
5. Roters S, Szurman P, Engels BF, Bartz-Schmidt KU, Krieglstein GK. Ultrasound biomicroscopy in chronic ocular hypotony: its impact on diagnosis and management. *Retina* 2002; 22(5):581-588.
6. Pleyer U, Ursell PG, Rama P. Intraocular pressure effects of common topical steroids for post-cataract inflammation: are they all the same? *Ophthalmol Ther*. 2013; 2(2):55-72.
7. Jones R III, Rhee DJ. Corticosteroid-induced ocular hypertension and glaucoma: a brief review and update of the literature. *Curr Opin Ophthalmol*. 2006; 17(2):163-167.
8. Vedantham V. Intraocular pressure rise after intravitreal triamcinolone. *Am J Ophthalmol*. 2005; 139(3):575.
9. Rhee DJ, Peck RE, Belmont J, et al. Intraocular pressure alterations following triamcinolone acetonide. *Br J Ophthalmol*. 2006; 90:999-1003.
10. Bollinger KE, Smith SD. Prevalence and management of elevated intraocular pressure after placement of an intravitreal sustained-release steroid implant. *Curr Opin Ophthalmol*. 2009; 20(2):99-103.
11. Jeng KW, Fine HF, Wheatley HM, Roth D, Connors DB, Prenner JL. Incidence of steroid-induced ocular hypertension after vitreoretinal surgery with difluprednate versus prednisolone acetate. *Retina* 2014; 34(10):1990-1996.
12. Wilson ME, O'Halloran H, VanderVeen D, et al. Difluprednate versus prednisolone acetate for inflammation following cataract surgery in pediatric patients: a randomized safety and efficacy study. *Eye (Lond)*. 2016; 30(9):1187-1194.
13. Giuffrè I, Taloni Mi, Babighian S, Alberti A. Thirty years of experience of ibopamine eye drops in ophthalmology. *Int J New Tech Res*. 2016; 2(12):38-42.

Butterfly Sutures for Temporary Closure of Sclerotomies

Claus Eckardt MD

According to the literature, the rate of sclerotomy suturing in 23- or 25-gauge vitrectomy is up to 38%.[1] Of course, every surgeon has their own individual rate, which is highly dependent not only on the technique but also on his or her specialization. Someone who performs mainly macular surgery naturally has a lower rate compared to a surgeon who is frequently presented with referrals of difficult cases and eyes with a failed prior vitrectomy. Other situations in which sutures are often used are high myopia, young age, prolonged surgical time, and silicone oil tamponade.

Polyglactin 910 (Vicryl 7-0, bzw 8-0, Ethicon, USA) is probably the most commonly used suture material for sclerotomies. Use of this material may occasionally lead to local inflammatory reactions and the sensation of a foreign body. Recently we therefore prefer using releasable sutures to close leaking sclerotomies, similar to those described by Lee and Song[2] and most recently by Arana et al.[3] In contrast to these authors, we use a monofilament 9-0 Vicryl suture, knotted with a double slipknot, whereby both loops resemble a butterfly. We use this suture only in cases where there is leakage after removal of the trocar, where leakage is anticipated, and in all eyes where a silicone oil tamponade is used. The knot can easily be removed postoperatively at the slit lamp.

We examined in more than 80 cases of 23-gauge transconjuntival vitrectomy whether it is possible to remove the butterfly suture on Day 1 postoperatively without complications. Among these eyes, some were with and some without gas tamponade, some had been repeatedly operated on, others were myopic, and some had silicone oil tamponade. In all eyes the IOP, measured 30 minutes and 6 hours after removal, remained stable compared to the IOP before removal. Furthermore, all cases underwent an OCT examination before and after suture removal, and no eyes showed an opening of the oblique tunnel incision after removal. Accordingly, these results show that removal of 9-0 Vicryl sclerotomy sutures may be performed on Day 1 postoperative without risk.

Selected Readings

1. Duval R, Hui JH, Rezaei KA. Rate of sclerotomy suturing in 23 gauge primary vitrectomy. *Retina* 2014; 34:679-683.
2. Lee BR, Song Y. Releasable suture technique for the prevention of incompetent wound closure in transconjunctival vitrectomy. *Retina* 2008; 28:1163-1165.
3. Arana LA, Moreira ATR, Grandinetti AA, et al. Novel vicryl releasable suture technique to clos leaking sclerotomies in a transconjunctival vitrectomy. *Retina*. In press.

Top 3 Avoidable Problems Leading to Redetachment

Failure Modes in Retinal Detachment Surgery

Steve Charles MD

I. Failure Mode
   A. Surgical
      1. Untreated retinal breaks / holes / tears
      2. Residual vitreous traction
   B. Biological: Proliferative vitreoretinopathy (PVR)
      1. Following appropriate surgery
      2. Iatrogenic

II. A Common Cause of Untreated Retinal Breaks and Residual Traction Is Poor Visualization
   A. Cataract

      Tradeoff: Combined phaco often results in miosis, which may require iris hooks, which increase inflammation; inflammation contributes to PVR.

   B. Posterior capsular opacification

      Tradeoff: Intraoperative capsulectomy results in IOL fogging after fluid–air exchange with all IOL materials, not just silicone; never remove central anterior vitreous if prior YAG capsulectomy.

   C. Use wide-angle visualization and/or scleral depression to ensure examination of peripheral retina.

III. Conceptualization Is a Key Aspect of Visualization
   A. Highest point of detachment may help find breaks (Lincoff rules).
   B. Concentric demarcation lines may point to retinal break(s).
   C. Patient's evolving "shadow" history may help locate initial retinal detachment and breaks.
   D. Localized pigmentation often indicates break location because of retinal pigment epithelium (RPE) apical process elongation and melanin migration (adaptive surface area increase to absorb subretinal fluid [SRF])
   E. Ends of lattice degeneration is common break location.
   F. In an optical effect known as "Schlieren," SRF may stream from break(s) during peripheral vitreous removal; it is not just a "core vitrectomy."
   G. Confluent laser to "suspicious" areas after internal drainage of SRF combined with fluid–air exchange often helps find breaks.

IV. Visualization of Residual Vitreous Traction
   A. Residual vitreous is easily seen during trans-hole or drainage retinotomy aspiration of SRF combined with fluid–air exchange.
   B. Remedy: Vitrectomy "under" air allows visualization of residual vitreous traction because of optical effect of vitreous interface with air (specular reflection / sheen and refractive effects).
   C. Marked, localized elevation of equatorial retina usually indicates residual vitreous traction.

V. Combining Scleral Buckling With Pars Plana Vitrectomy Is *Not* the Answer
   A. *No* randomized clinical trial evidence that combining a buckle with vitrectomy increases success rates compared to pars plana vitrectomy alone.
   B. New breaks and PVR often occur posterior to encircling bands; even broad buckles.
   C. Buckle complications:
      1. Induced axial myopia (unhappy patient if prior LASIK, PRK, or refractive cataract surgery)
      2. Increased phorias and tropias
      3. Longer operating times, increased labor cost, more general anesthesia use, pain
      4. Ocular surface disorder from poor conjunctival closure
      5. Slight ptosis from levator aponeurosis damage
      6. Conjunctiva, Tenon, and episcleral scarring cause problems if subsequent glaucoma surgery is required.
      7. Buckle extrusion

VI. Rows of 360° Laser Are Not the Answer
   A. Increased inflammation; possibly increased PVR
   B. Toroidal (donut) detachment between equatorial or post-equatorial laser and ora serrata
   C. Increased PVR
   D. Anterior segment neovascularization from VEGF produced by chronically elevated anterior retina
   E. Breaks missed at surgery and/or new breaks often occur between laser spots or posterior to laser spots.

VII. Iatrogenic Causes of PVR

A. Excessive retinopexy; both quantity / area of applications and intensity

B. Cryopexy causes more inflammation and PVR than laser does.

C. Too little time between surgical procedures; do not operate on "hot" eyes.

VIII. Do Not Leave Capsule for Subsequent IOL Insertion If Lensectomy Performed

A. Capsule becomes adherent to iris and residual anterior vitreous.

B. IOL insertion *never* happens.

C. Concave iris

D. Fixed pupil

E. Probable increased anterior PVR secondary to increased inflammation and capsule-cortex-peripheral vitreous adherence.

F. Inferior iridectomy closure in silicone oil cases secondary to fibrosis unless total capsule removal with forceps.

IX. Confluent Laser Retinopexy Is Better Than Spots

A. Spots are an outdated idea apparently related to cryo and diathermy retinopexy because these probes cannot be moved while energy is applied.

B. Endolaser produces a top-hat (square) beam profile that produces hot center and cold surrounding tissue heating, and therefore nonuniform healing and adherence.

C. Spots produce undesirable overlapping (excessive damage) or underlapping (adherence gaps enabling SRF leakage).

D. Moving the laser while surrounding retinal breaks utilizes motion blur to produce more uniform lesions without gaps.

X. Critical Elements of Successful Surgery

A. Must use wide-angle visualization

B. Must use scleral depression if non-contact wide-angle visualization

C. Remove vitreous traction from flap of all flap tears and anterior to all breaks.

D. Remove as much peripheral vitreous as possible without damaging clear lens.

E. Surround all breaks with moderate intensity confluent laser, *not* rows of spots.

F. Do not hesitate to remove lens or IOL if poor view.

G. No combined phaco

H. Do not leave capsule if lensectomy.

I. No 360° laser

J. No buckles

K. Make use of medium-term perfluoro-n-octane PFO for inferior retinal detachments (PFO causes gentle PVD creation over 2 weeks in young myopes without PVD; remove posterior vitreous cortex when PFO removed).

L. If "hot" eye, use silicone oil and perform laser later.

M. Do not remove central anterior vitreous if prior YAG.

Pearls for Large Macular Holes

Carl Claes MD

Many surgical variations for macular hole repair have been introduced since the presentation of the first surgical successes by Kelly and Wendel.

- Vitrectomy + gas ± positioning
- Vitrectomy ± internal limiting membrane (ILM) peeling
- Vitrectomy ± ILM flap manipulation
- Vitrectomy + silicone oil
- Ocriplasmin injection
- Gas injection
- Vitrectomy + retinal redistribution
- Vitrectomy + retinal flap transplantation

Every variation has its indication and possible side effects. Surgeons should customize the technique according to the characteristics of the hole and their experience.

The Retinal Redistribution Technique for Very Large, Myopic, or Failed Macular Holes

The described technique was developed to treat very large macular holes (800-1500 microns) primarily, as well as failed cases. The presence of ILM is not required to obtain anatomical repair. Also the absence of a cuff of subretinal fluid does not influence the indication of surgery.

The surgery is done in the pseudophakic eye.

1. A regular vitrectomy is performed with a careful detachment of the posterior hyaloid if not already present. In highly myopic eyes, triamcinolone will be injected to detect hyaloidal remnants.
2. The next step consists of ILM peeling with help of brilliant blue.
3. A perfluoro-decalin (Decaline) bubble is placed over the hole.
4. Brilliant blue is applied drop by drop, by fingertip compression on a flute needle reservoir that contains the dye.
5. Furthermore, the bubble of perfluoro-decalin prevents subretinal migration of dye via the macular hole.
6. After ILM removal, the retina is detached from the pigment epithelium in the posterior pole by injection of subretinal BSS trough a 40-gauge needle.
7. The perfluoro-decalin bubble prevents leakage of the subretinal BSS via the hole, in this way promoting the spreading of the iatrogenic retinal detachment toward the arcades and beyond.
8. When the retina is detached for 360 degrees several disc diameters around the macular hole air–fluid exchange is performed, perfluoro-decalin is aspirated, and the subretinal fluid is drained through the hole.
9. The removal of subretinal fluid is performed with a 30-gauge flute needle with tapered shaft, especially designed for this purpose. A lot of care is taken not to engage the edges of the macular hole, and to avoid damaging the pigment epithelium with the tip of the instrument.
10. The next step consists of an injection of 1000-cs silicone oil, with special attention to the complete drainage of the BSS collected underneath the silicone oil bubble and the remaining submacular fluid. This maneuver is again executed with the previously mentioned 30-gauge tapered flute needle.
11. The removal of the perimacular BSS induces the approximation of the edges of the hole.
12. Repetition of this maneuver will result in closure of the hole intraoperatively.
13. The surgery is finished when the edges of the hole are approximated.
14. The silicone oil tamponade is removed after 6 weeks.

Six eyes with holes size ranging from 800 to 1500 microns were treated accordingly. Anatomic and functional improvement were obtained.[1]

Reference

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Tips for Myopic Eyes

Hiroko Terasaki MD

Introduction

Myopic traction maculopathy (MTM) is believed to represent prodromal stages of macular hole (MH) retinal detachment (MHRD). Vitrectomy is a common treatment modality for these prodromal stages in an attempt to prevent the development of MHRD. Unfortunately, there are many patients who develop MH or MHRD. Eyes affected by the latter condition are usually immediately indicated for surgery.

MTM or MH/MHRD might be one serious and stressful surgical treatment indication among various conditions for vitrectomy due to the long axial length of these eyes, with posterior staphyloma, thinner nerve fiber layer, atrophic retina even with increased retinal thickness, higher incidence of glaucoma, and postoperative complications such as MH formation or MHRD development after vitrectomy for MTM, or unclosed MH after MHRD surgery. Some practical tips would be helpful to overcome the problems arising from these issues.

Tips

I. Measurement of Axial Length and Choice of Instrument

Choosing the appropriate instrument is essential. In longer eyes, instrument flexibility is a problem—for example, 27-gauge would be very flexible for longer eyes, but with 23-gauge, there will be leakage around the sclerotomy, and 25-gauge instruments would be most commonly used in such highly myopic eyes. In eyes with schisis-like structure (schisis) or MHRD, the retina is elevated, and regular inner limiting membrane (ILM) forceps can reach the retinal surface even in a long eye. Eyes with MH without schisis might need longer instruments instead. To remove the subretinal fluid in eyes with MHRD, a long-shaft back-flash needle will be needed for eyes longer than 30 mm.

II. Correct Staging Using OCT

Because of the longer axis with deep staphyloma and increased thickness of the retina in MTM, correct diagnosis can be made using suitable spectral domain OCT technique; eg, enhanced depth imaging mode and upper positioning of the image of the staphyloma. Using swept source OCT, good quality images can be obtained every time because of the wide depth of focus (see Figure 1).

Surgery for MTM

- MTM includes the following: epiretinal membrane, pseudohole without schisis, schisis with/without foveal detachment (FD), and MH with/without schisis.
- Check the presence or absence of FD or MH.
- Ensure that the thickness of the nerve fiber layer and visual field are sufficient for the eye to undergo surgery.

Surgery for MHRD

- If the macular hole is not found in eyes with posterior RD, paravascular hole may be present.
- Thin slice vertical OCT is useful in detecting this hole.

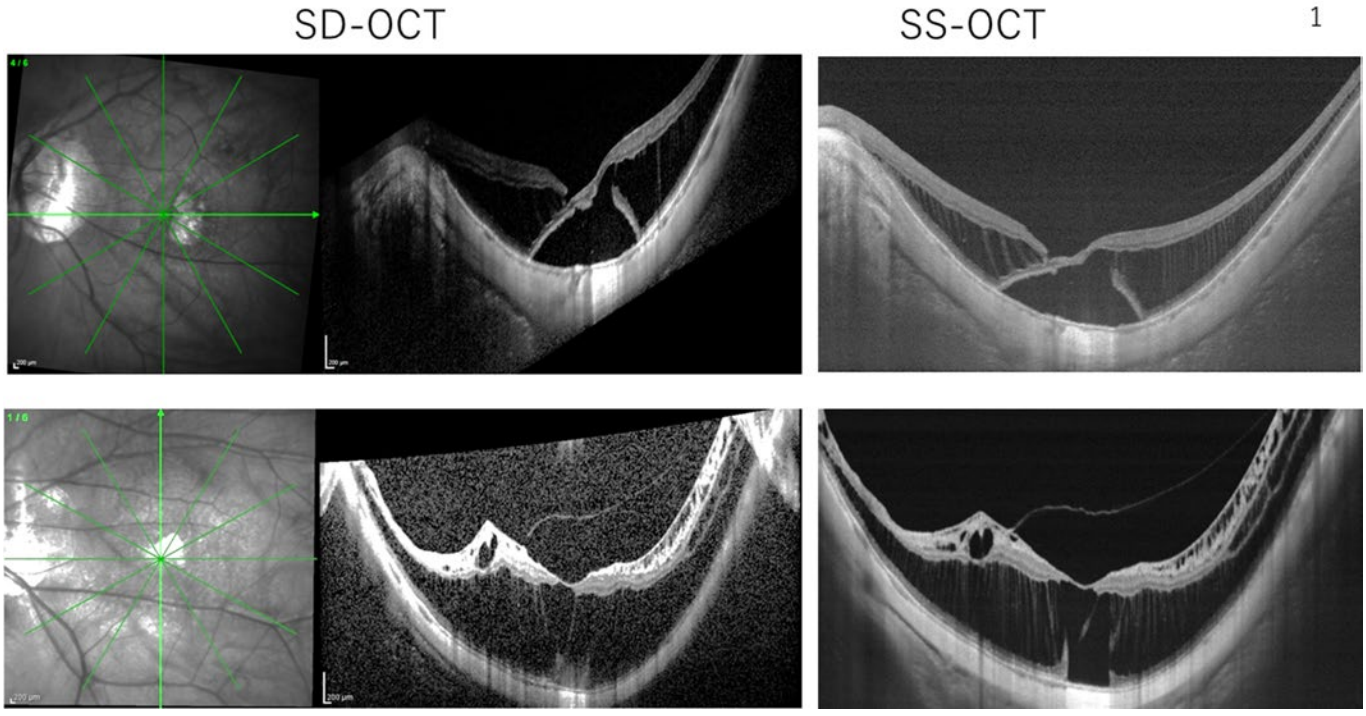

Figure 1.

III. Surgical Method Selection

Schisis with/without FD:

The development of MH after surgery has been reported in approximately 15%-30% of individuals (Shimada et al, *AJO* 2012; Gao et al, *AJO* 2013; Ho et al, *Retina* 2014) and in 5% of individuals in our series (Hattori et al, *Retina* 2017) with standard vitrectomy and total ILM peeling. Recently, the foveola-nonpeeling (Ho et al, *Retina* 2012; Ho et al, *Retina* 2014) or fovea-sparing (Shimada et al, *AJO* 2012) technique has been reported for myopic schisis. In these studies and in our recent series of fovea-sparing technique, all the eyes with FD did not develop postoperative MHs. Because total peeling is easier than the fovea-sparing technique, the indication for this technique may be limited to the eyes with schisis with FD. If the ellipsoid zone is continuous on the clear image of OCT, gentle total ILM peeling will not cause postoperative MH. In our series, no MH developed in eyes with schisis alone.

MH with/without schisis:

To improve the anatomical results, inverted ILM flap technique (Michalewska et al, *Ophthalmology* 2010) has been indicated for myopic MH (Kuriyama et al, *AJO* 2013; Hayashi et al, *Retina* 2014; Michalewska et al, *Retina* 2014). In our series, the minimum size of flat/open MH after the first surgery was > 500 microns, which may indicate the inverted ILM flap technique.

In a recent large case series of MH including 620 eyes, the success rate of MH closure in the eyes with axial length of ≥ 26 mm was better with the inverted flap technique (40.0% with total peeling vs. 88.5% with inverted flap technique) (Rizzo et al, *Retina* 2017). In their series, successful closure of MH in eyes with axial length of < 26 mm was 94.3% with total peeling and 93.8% with inverted flap technique.

MHRD:

To prevent flat/open MH, which is the cause of poor postoperative visual acuity or RD recurrence, the inverted ILM flap technique has been developed. As the closure rate of MH with RD using standard vitrectomy is not high, the inverted flap technique may be indicated as a common technique for treating *all* eyes with MHRD.

IV. Surgical Methods and Tips for ILM Management

There are many techniques to cover or seal MHs (see Table 1). In a highly myopic eye, even Weiss ring is present, and the large posterior vitreous membrane is covered throughout the posterior pole. Hence, the surgery begins with peeling the posterior vitreous membrane and may occasionally resemble ILM.

1. Remove the posterior vitreous membrane first

Remove the posterior vitreous membrane first, separately from ILM removal, after injecting the triamcinolone particle. The posterior vitreous membrane is sometimes soft or membranous like thick ILM. A soft posterior vitreous membrane can be removed easily with diamond-dusted eraser (see Figure 2).

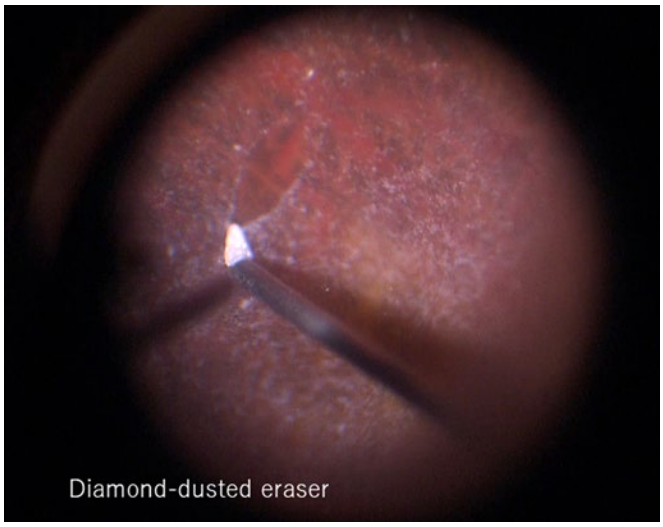

Figure 2.

Table 1 Variation of ILM Flap Technique for MH or MHRD

Classic (multi-layered ILM flap)

- Kuriyama S, et al. AJO 2013
- Michalewska Z, et al. Retina 2014

Single layer (including not for myopic)

- Inferior flap Song Z, et al. J Ophthalmol 2016
- Superior flap Choi SR, et al. Retina 2017
  Chen SN, et al. Graefes 2017
- Temporal flap Michalewska Z, et al. Retina 2015
  Ho TC, et al. Acta 2017
- Pedicle flap Gekka T, et al. OSLIR 2015
- Lens capsular Chen SN, et al. Retina 2016

Insertion

- Chen SN, Yang CM. AJO 2016
- Olenik A, et al. Retina 2016
- Theodossiadis GP, et al. AJO 2016
- Rossi T, et al. Graeafes 2017

Adjuvant

- BBG/TA ICG?
- Platelet-rich plasma Figueroa MS, et al. Eur J Ophthalmol 2016
- Blood Lai CC, et al. Ophthalmology 2015
- PFCL Shin MK, et al. Retina 2014
- Ovd Song z et al. J Ophthalmo 2016

2. ILM is always present

ILM is always present after 1 membrane is removed, which may be occasionally similar to ILM. Pick ILM near and inside the inferior arcade vessel without damaging the superior retina, which is more sensitive to the visual field.

3. ILM staining

To remove ILM, brilliant blue G and triamcinolone are used as adjuvants. In a highly myopic eye, the retinal nerve fiber layer is thinner than that in a nonmyopic eye. Of note, any dye enhances phototoxicity by illumination, even with brilliant blue G.

4. Foveal-sparing ILM peeling for MTM with FD

ILM is removed from the surrounding to the center but stopped at 1 disc diameter from the foveal area. After trimming with a cutter as short as possible, further peeling of the ILM is performed as close as possible till the edge of the FD area, and further trimmed as short as possible. A cutter port should be faced toward the opposite of the fovea during trimming (see Figure 3). Intraoperative OCT may be helpful to visualize the remaining area (Figure 4).

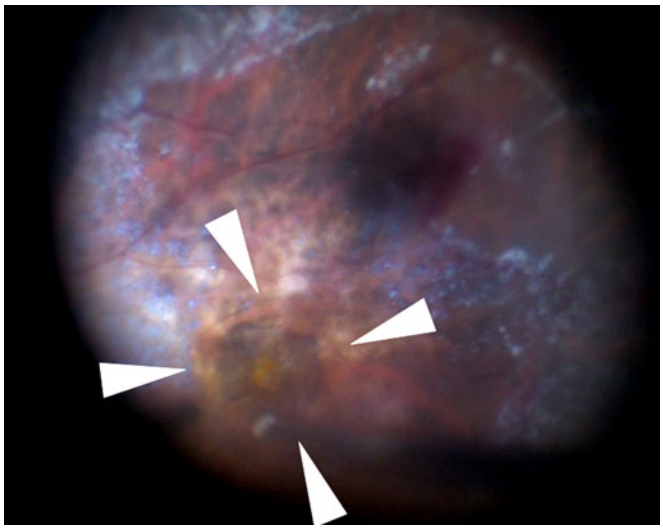

Figure 3. Fovea-sparing internal limiting membrane peeling.

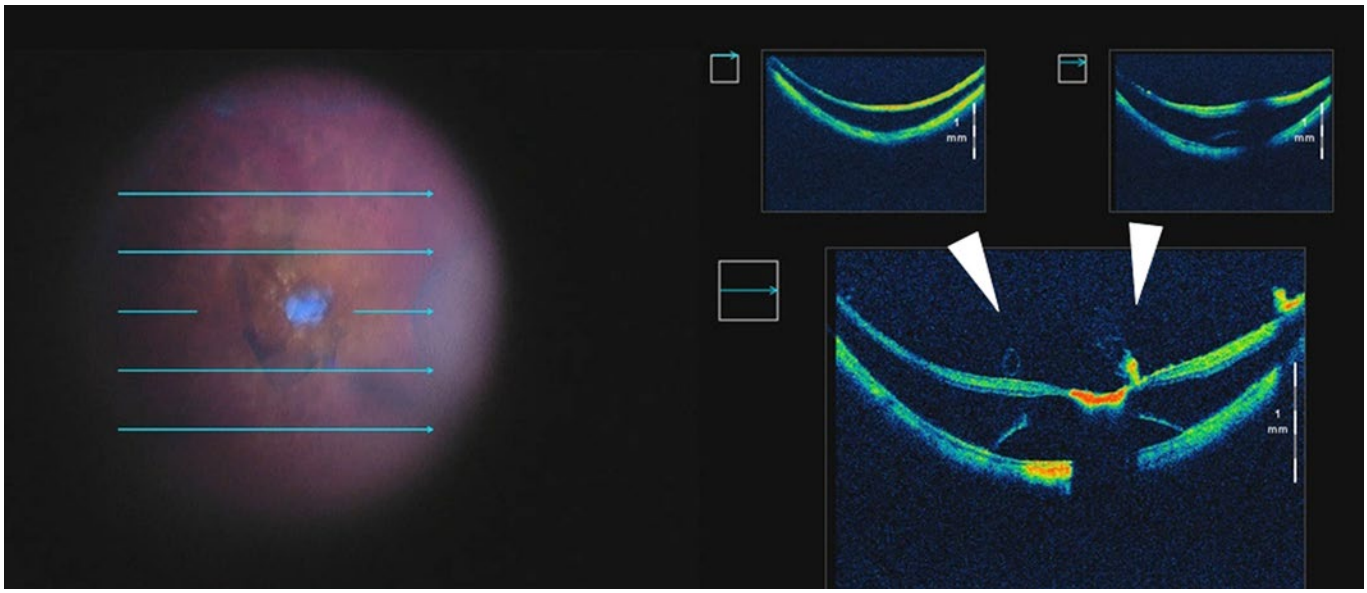

Figure 4. Intraoperative OCT.

5. Inverted ILM flap insertion for MH and MHRD

For the flap, a relatively large ILM should remain. Therefore, after picking the ILM, peeling up to 2 disc diameters from the fovea, trimming it with a cutter, and further peeling up to the edge of MH are performed. The remaining ILM is inserted into MH using a diamond-dusted eraser (Figure 5). Intraoperative OCT shows multi-layered ILM in the hole (Figure 6).

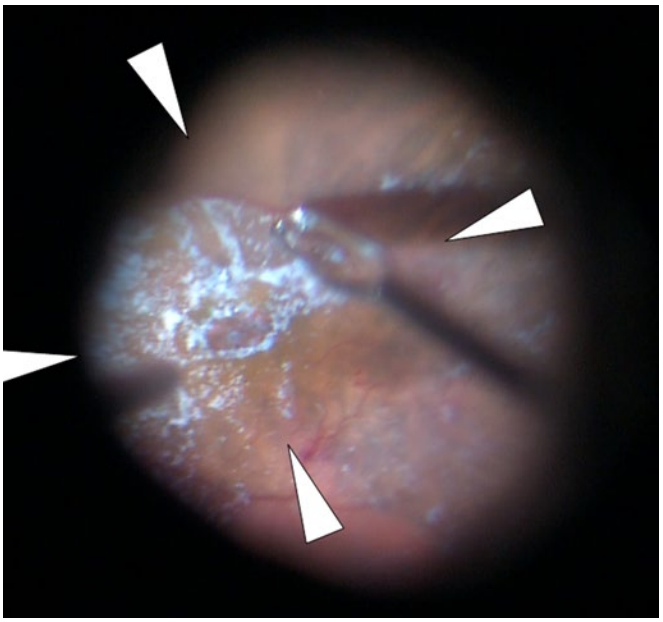

Figure 5. Inverted internal limiting membrane flap technique for a large myopic macular hole.

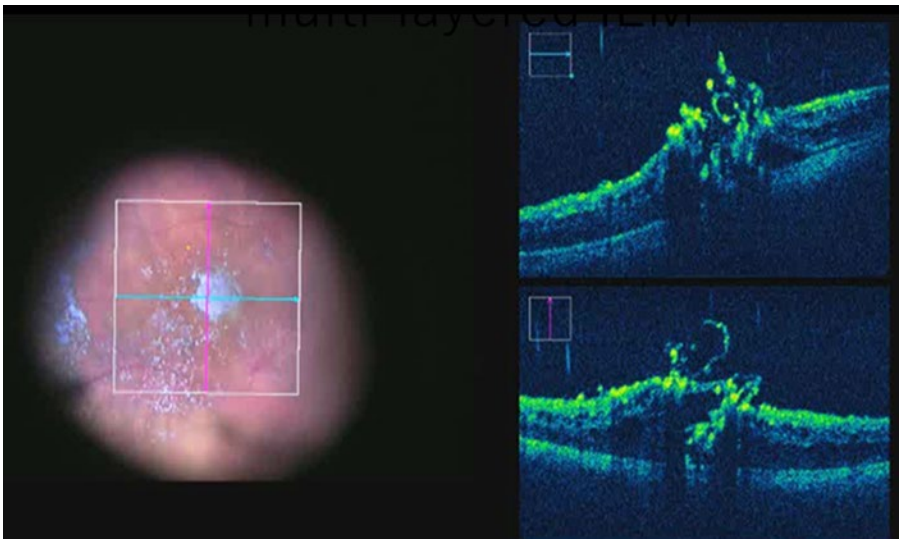

Figure 6. Intraoperative OCT.

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A New Way to Close Holes and Breaks

Stanislao Rizzo MD

Purpose

To describe the surgical outcomes of 9 patients treated for persistent macular hole and rhegmatogenous retinal detachment using a novel biocompatible film to promote repair of retinal breaks and closure of macular holes.

Methods

Three patients with retinal detachment and 6 patients with persistent macular hole underwent pars plana vitrectomy with internal limiting membrane peeling and gas tamponade without resolution, followed by pars plana vitrectomy and implant of the biocompatible film in the macular hole / retinal break area; no laser retinopexy was carried out for retinal breaks. Silicone oil was used in retinal detachment and SF_6 in macular holes. Silicone oil was removed after 3 months in all cases.

Results

Successful retinal reattachment and macula hole closure was achieved in all 9 eyes.

No retinal detachment developed proliferative vitreoretinopathy. After silicone oil removal, no epiretinal membrane proliferation was observed after vital dying staining. No laser retinopexy was applied even after silicone oil removal. We observed retinal breaks sealing with a thin membrane.

Mean BCVAs were 20/1000 and 20/400 preoperatively and 20/32 and 20/50 postoperatively in retinal detachment and macular hole groups, respectively.

We had no postoperative complications.

Conclusions

The film promotes retinal break closure without laser retinopexy and macular hole closure as with the autologous ILM transplantation technique.

No adverse events were noticed during the follow-up period.

Hypersonic Vitrectomy: Continued Clinical Experience and Technical Improvements

2018 Update

Carl C Awh MD

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

During the fall of 2017, Drs. Carl Awh and Kevin Blinder performed a consecutive case series of 84 vitrectomies. Sixty-four were performed using a 23-gauge hypersonic vitrectomy device and 20 with a conventional 23-gauge vitrectomy device. No statistically significant differences in irrigation fluid volume, time of device activation, or time of active aspiration were found.

Preoperative diagnoses included the following:

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

One iatrogenic retinal break in an area of mobile detached retina and 1 case of unintended scoring of the posterior surface of an acrylic IOL during capsulotomy were the only reported intraoperative complications. All cases were successfully completed with both the hypersonic and conventional cutters.

The hypersonic cutter design has been modified since the fall of 2017. The new probes have been tested in vitro, and the flow through 27-, 25-, and 23-gauge probes has been found to be equivalent to that of a bidirectional guillotine cutter, despite the fact that the port area of the hypersonic cutter is only one-third that of the guillotine cutter.

By the time of the AAO 2018 Retina Subspecialty Day meeting, the modified hypersonic vitrectomy device will have been used in humans, and additional information will be presented.

Development of a Deep Learning System for Digitally Enhanced Internal Limiting Membrane Peeling

Kazuaki Kadonosono MD

Introduction

We proposed to investigate a deep learning approach[1] to accurately identifying the internal limiting membrane (ILM) during vitreoretinal surgery, while minimizing the use of dyes. ILM peeling is an invaluable surgical procedure used to treat macular holes and/or other retinal diseases such as epiretinal membrane, diabetic macular edema, and proliferative vitreoretinal (PVR) diseases. To assist in visualization during the procedure, the ILM is routinely stained with dyes, including indocyanine green and brilliant blue G, allowing surgeons to remove the ILM more effectively. However, even ILMs that have been stained with dyes can be difficult to observe in eyes with particular types of membranes, such as highly myopic eyes and those with diabetic macular edema or PVR. The concentration and exposure time of dyes is another issue, causing damage to retinal cells such as retinal pigment epithelial cells and photocells.[2] Therefore, it is necessary to reduce the concentration of dyes used in the ILM staining procedure, while establishing a method to more clearly observe the ILM, resulting in easier removal.

Background Observations

Recently developed digitally assisted vitreoretinal surgery allows us to observe the ILM more clearly utilizing digital technology. Digitally enhancing the ILM by changing digital parameters such as HUE has proven useful, allowing surgeons to more easily differentiate the ILM from underlying layers. Software that uses a special algorithm to aid enhancement has also been developed; however, there are still some limitations when treating eyes with myopia or pathological ILM. In this study, we used an automated artificial intelligence method[3] to analyze images of the macular region, which had been intraoperatively stained with a dye. Deep learning methods have been recently suggested for automated detection of diabetic retinopathy from fundus images.[4]

The images used had a maximum size of 3.0 x 3.0 mm^2 with a fovea present in the center. All images were drawn for the presence of ILM in a quality-controlled reading center setting by 2 experienced independent retinal specialists. The 16-segmentations approach was used, and the neural network assigned an input image of a particular size to an image of corresponding class labels of the same size. The neural network comprised 2 processing components, an *encoder* that transformed an input image into a *decoder* that maps the abstract representation to an image of figures presenting each pixel a class.

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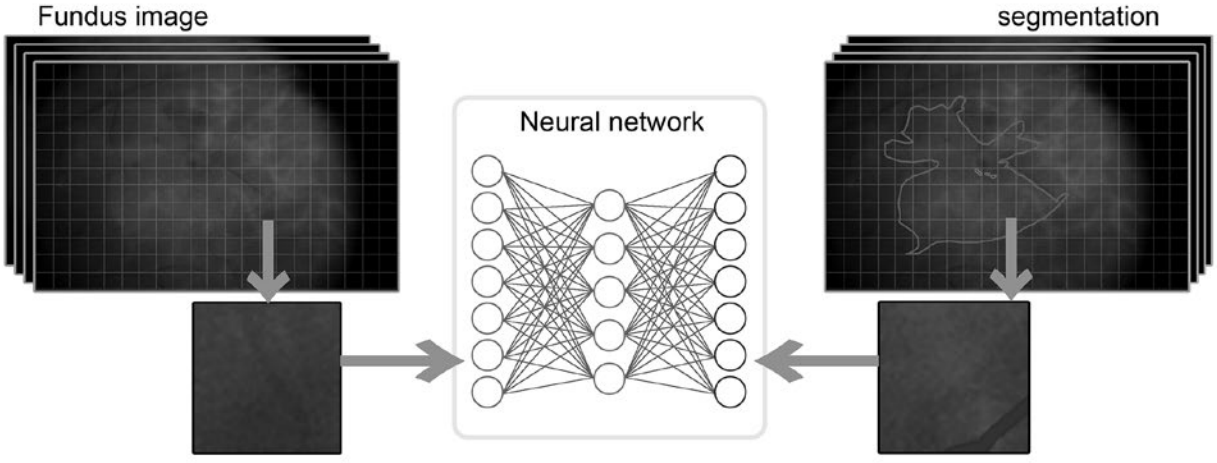

Figure 1. A picture of the automated method. The approach comprises a convolutional neural network with an encoder-decoder architecture to identify the internal limiting membrane (ILM). The *encoder* maps an intraoperative image to an abstract representation (embedding). The *decoder* maps this embedding to a full input resolution label image with a curved line and a figure (ILM).

Final Visual Acuity, Not Amount of Improvement, Must Be the Measure of Our Success in Epiretinal Membrane Surgery

Colin A McCannel MD

NOTES

Management of Complications Correlated With the Use of Intraocular Tamponade

Grazia Pertile MD

Introduction

An intraocular tamponade provides a filling of the vitreous cavity and, ideally, leaves the anterior chamber (AC) unaffected. To maintain the tamponade confined in the vitreous cavity, the aqueous humor should be produced in sufficient amount and flow freely towards the AC angle. If the AC is altered, it is necessary to take into consideration a number of factors (kind of tamponade, IOP, lens status, presence / patency of an iridectomy) in order to be able to identify the cause and manage the complication.

Main Complications

I. Silicone Oil in the AC

A. High IOP

1. Aphakic eyes

a. Iridectomy (6 o' clock) closed → Open it

b. Iridectomy (6 o' clock) open → Possible overfilling—consider surgical revision

2. Pseudophakic or phakic eyes

a. No iridectomy required, unless 360° synechiae are present

b. Surgical removal necessary; no chance for it to go back into the vitreous cavity

B. Normal IOP

1. Aphakic eyes

a. Iridectomy (6 o' clock) closed → Open it.

b. Iridectomy (6 o' clock) open → Leave it like it is. If the aqueous production is enough, silicone oil will go back into the vitreous cavity.

2. Pseudophakic or phakic eyes: Surgical removal of the silicone oil and simultaneous replacement with a dispersive viscoelastic material is recommended.

C. Low IOP

1. Aphakic eyes

a. Iridectomy (6 o'clock) closed → Open it. Silicone oil will go back to the vitreous cavity if the aqueous production is sufficient to fill the AC.

b. Iridectomy (6 o'clock) open → Leave it like it is. This is a sign that the aqueous production is not enough to maintain the AC.

2. Pseudophakic or phakic eyes

a. Surgical removal and simultaneous replacement with a cohesive viscoelastic material

b. An iridectomy will not help as the aqueous production is insufficient to maintain the AC

II. Heavy Silicone Oil in the AC

Same flow chart as for silicone oil except that the iridectomy position that should be at 12 o'clock instead of at 6 o'clock.

III. Shallow AC in a Gas-Filled Eye

A. High IOP

1. Aphakic eyes

a. Iridectomy (6 o' clock) closed / absent (pupillary block) → Make one or dilate the pupil.

b. Iridectomy (6 o' clock) open → Possible overfilling (expansible gas mixture); consider venting some gas if the IOP cannot be controlled with medication.

2. Phakic and pseudophakic eyes: Possible overfilling, consider venting some gas in case of uncontrolled IOP.

B. Normal or low IOP: No action needed

IV. IOL Dislocation in a Gas-Filled Eye

Wait for gas reabsorption before IOL repositioning.

Vitrectomy for Diabetic Macular Edema: Why, How, and When

Gaurav K Shah MD

I. Introduction

A. Diabetic macular edema (DME) is the leading cause of visual impairment in developed nations.[1,2]

B. Mainstay of therapy for DME includes intravitreal anti-VEGF agents.

C. There is no standardized approach for the treatment of chronic or recurrent DME, and repeated intraocular injections pose a significant burden on patients, physicians, and the health-care system.

II. Pars Plana Vitrectomy (PPV) for DME: Why?

A. Pathology at vitreoretinal interface: Eyes with posterior vitreous detachment (PVD) develop DME less frequently than eyes with attached hyaloid.

B. Vitreous may harbor inflammatory mediators contributing to DME.

C. Relieving tractional forces may help with:

1. Anatomic improvement of vitreomacular traction

2. Oxygenation of tissue may favor arteriolar constriction.

III. PPV for DME: How?

A. With or without internal limiting membrane (ILM) peeling

1. A prospective study indicated that ILM removal, compared to PVD induction with PPV alone for DME, stabilized visual acuity and improved cystoid macular edema.[3]

2. ILM removal stabilized BCVA and morphological results.

B. ILM plays a role in pathology.

1. ILM is 2 times thicker in DME cases than in macular hole cases.[4]

2. ILM peel may stimulate glial tissue healing.[5]

IV. PPV for DME: When?

A. Some advocate for PPV for patients who have "persistent DME,"[6] defined as:

1. Central macular thickness (CMT) > 250 µm

2. History of 2 sessions of either macular photocoagulation or intravitreal anti-VEGF

B. Some studies suggest earlier PPV before unfavorable spectral domain OCT findings . ELM and ellipsoid zone (IS/OS) integrity correlates with postoperative outcome.[7]

V. Conclusions

A. DRCR.net PPV study provided a reference for surgical intervention for DME.[8]

B. New studies indicate that PPV may be an appropriate and safe[9] option for DME treatment.

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Myopic Foveoschisis

Ramin Tadayoni MD PhD

Background

Myopic foveoschisis, also known as myopic retinoschisis and myopic traction maculopathy, is a complication of high myopia. Its prevalence in high myopes has been reported to be, depending on the series, around 10%-30%.

Which Myopes Are at Risk?

While the pathophysiology of myopic foveoschisis is not fully understood, this complication occurs only in deep staphylomas where the retina seems stretched between a growing sclera and more rigid internal layers. Highly myopic eyes (> 6 D refractive error or ≥ 27 mm axial length) with a staphyloma involving the macula can then develop a myopic foveoschisis.

What Are the Symptoms?

Many patients are asymptomatic despite a significant myopic foveoschisis. Others present various degrees of visual loss. Metamorphopsia or scotomas are uncommon unless a macular hole or macular detachment occurs on top of the myopic foveoschisis.

How Is the Diagnosis Made?

The diagnosis can be made in some cases during a fundus examination, by observing in the macular area a retinal detachment without macular hole in high myopia as described in 1958.[1] However, more often it is an OCT diagnosis.[2] OCT scans show a thickening of the macula at the bottom of a staphyloma. In addition, the macula seems stretched, with nonreflective spaces in different layers of the retina, in particular the Henle fiber layer, where the retina appears as forming numerous column-like structures. On the surface of the retina a membrane can be associated. We have also shown that often the vitreous is still attached in these eyes.[3] A macular hole can also complicate the myopic foveoschisis in some cases, as the fovea can detach and the detachment can then spread.

Workup

Medical history, evaluation of symptoms and the induced handicap, visual acuity measurement, OCT and fundus photos (color and autofluorescent to evaluate in particular the extent of any chorioretinal atrophy), and any other imaging to exclude a suspected concomitant complication of high myopia are necessary for deciding on the management. Indeed, as many foveoschises may be paucisymptomatic or asymptomatic and since myopic eyes may combine complications, one should always consider various differential diagnoses for these patients' symptoms.

Which Eyes Should Be Offered Surgery?

Severe decrease in visual acuity and metamorphopsia due to a secondary macular hole or a scotoma due to a macular detachment obviously are indications for surgery. On the other hand, patients presenting with a myopic foveoschisis and normal vision can benefit from observation, as they may continue to have good vision for years.[4] In between, many patients present with a myopic foveoschisis with variable degrees of visual impairment, and the right time to propose surgery to them remains unclear.

In a large multicentric series of myopic foveoschises, we have shown that the main predictive factor for actual final visual acuity of these eyes is the BCVA at the time of surgery, with those operated at 20/50 or better achieving a mean postoperative visual acuity of 20/30. This has to be put in balance with a delicate surgery that can lead to complications and loss of vision (10.6% in the whole population of our series). However, these complications occurred mainly in low visual acuity eyes, and the surgery having progressed it is more and more often proposed at a higher visual level than it used to be.[5]

The Surgery

The principles of vitreoretinal surgery of myopic foveoschisis are to peel anything on the surface of the macula (hyaloid, membrane, and internal limiting membrane) that prevents the retina from going toward the back of the eye, while avoiding complications. If a hole is present a tamponade is also used.

Surgery for myopic foveoschisis has greatly benefitted from recent progress made in vitreoretinal surgery—from machines and instruments to visualization. Staining has considerably facilitated surgery in these eyes, where interfaces are abnormal and visibility low. More recently, we have shown that intraoperative OCT can be of significant help during surgery by displaying critical information that our eyes cannot see in these eyes.[6] Myopic foveoschisis has been also a vibrant area of technical innovation and experimentation: macular buckling, fovea-sparing internal limiting membrane peeling, and internal limiting membrane flaps (if an associated hole) are among the many innovations surgeons use today to push the limits of this surgery.

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Developing Therapies for AMD: The Art and Science of Problem Solving

Joan W Miller MD

I. Problem Solving
   A. Defining the problem
   B. Analysis and insight
   C. Planning and serendipity
II. Why Develop Therapies for Neovascular AMD First?
   A. Treatment options in the 90s
      1. Laser photocoagulation
      2. Surgical removal and translocation
III. Development of Photodynamic Therapy
   A. An old therapy rejuvenated
   B. Eureka moments
IV. Development of Anti-VEGF
   A. Searching for Factor X
   B. Treating AMD was a stretch—but a successful one.
V. Biology-Based Treatments for AMD
   A. Success in treatment, as therapy targeted key pathway (VEGF mediator of angiogenesis)
   B. Therapies for early disease require better understanding of AMD pathogenesis: clinical observation and imaging, epidemiology, histopathology, genetics and molecular biology
VI. How Do We Approach Treating Early and Intermediate AMD?
   A. To treat early and intermediate AMD we have to understand it.
      1. Identify key pathways and potential therapeutic targets in those pathways
      2. Improve our understanding of structure / function and biomarkers
   B. This may lead to reclassification and delineation of subtypes of early and intermediate AMD.
VII. Current Understanding of Key AMD Pathways—Potential Areas of Target for Intervention
   A. Inflammation and immunity
      1. Complement
      2. Inflammasome
   B. Lipid deposition / metabolism
   C. Aging and senescence: autophagy
   D. Anti-angiogenesis
      1. Do we need additional anti-angiogenic therapies beyond anti-VEGF? (platelet-derived growth factor, angiopoietin–TIE)
      2. Anti-VEGF controls neovascular AMD, but neurodegeneration is unchanged.
   E. Neuroprotection
      1. Necessary to protect photoreceptors
      2. Multiple cell death pathways
         a. Complementary and redundant
         b. Combination therapy to inhibit multiple cell death pathways simultaneously
      3. Potential to be used in concert with anti-angiogenesis treatment
VIII. Refining Our Understanding of AMD Pathways
   A. Structure / function correlation: Imaging, tissue, and 'omics
   B. Metabolomics as a biomarker
   C. Structure-function changes
   D. May lead to reclassification
IX. Conclusions

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2018 Advocating for the Profession and Patients

Retina Subspecialty Day

Sohail J Hasan MD PhD

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

Please join the dedicated community of ophthalmologists who are contributing to protect quality patient eye care for everyone. The OPHTHPAC Committee is identifying Congressional Advocates in each state to maintain close relationships with federal legislators in order to advance ophthalmology and patient causes. At Mid-Year Forum 2018, we honored nine of those legislators with the Academy's Visionary Award. This served to recognize them for addressing issues important to us and to our patients. The 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 the OPHTHPAC Fund. Each of us has a responsibility to ensure that these funds are strong.

OPHTHPAC® Fund

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

Advocating for our issues in Congress is a continuous battle, and OPHTHPAC is always under financial pressure to support our incumbent friends as well as to make new friends among candidates. These relationships allow us to have a seat at the table with legislators who are willing to work on issues important to us and our patients.

The relationships OPHTHPAC builds with members of Congress is contingent on the financial support we receive from Academy members. Academy member support of OPHTHPAC allows us to advance ophthalmology's federal issues. We need to increase the number of our colleagues who contribute to OPHTHPAC and to the other funds. 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.

Among the significant impacts made by OPHTHPAC are the following:

- Secured relief from the burdens and penalties associated with the existing Medicare quality improvement programs for 2018
- Halted applications of MIPS penalties to Part B drug payments to physicians
- Convinced CMS to revisit drastic cuts to retina and glaucoma surgical codes
- Halted the flawed Part B Drug Demonstration
- Derailed an onerous global surgery payment data collection plan
- Continued efforts in collaboration with subspecialty societies to preserve access to compounded and repackaged drugs such as Avastin

Contributions to OPHTHPAC can be made here at AAO 2018, or online at www.aao.org/ophthpac by clicking "Join." You can also learn more by texting "OPHTH" to 51555.

Leaders of the three retina societies—the American Society of Retina Specialists (ASRS), the Macular Society, and the Retina Society—are part of the American Academy of Ophthalmology's Ophthalmic Advocacy Leadership Group (OALG), which meets annually in January in Washington, D.C., to provide critical input and to discuss and collaborate on the Academy's advocacy agenda. At the January 2018 OALG meeting, panel discussions took place on the outlook for Medicare reimbursement and implementation of the Merit-based Incentive Payment System (MIPS), as well as specialty research related to the IRIS™ Registry. In addition, meeting participants discussed the changing paradigm for optometric scope battles, held a roundtable to discuss challenges for surgical subspecialties, and considered how telemedicine could impact ophthalmology.

At Mid-Year Forum 2018, 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 ASRS, the Macula Society, and the Retina Society remain crucial partners with the Academy in its ongoing federal and state advocacy initiatives.

Surgical Scope Fund

Thanks to contributions to the 2018 Surgical Scope Fund (SSF) from ophthalmologists across the country, the Academy's Surgery by Surgeons initiative has had a successful year preserving patient surgical safety and surgical standards in state legislatures across the country. The SSF is key to the Academy's Surgery by Surgeons campaign. *If you have not yet made a 2018 SSF contribution*, visit our contribution booth at AAO 2018 or contribute online at www.aao.org/ssf. If you already have made that 2018 contribution, please consider making a crucially needed supplemental contribution.

The SSF provides grants to state ophthalmology societies in support of their efforts to derail optometric surgery propos-

als that pose a threat to patient safety. Since its inception, the Surgery by Surgeons campaign and the SSF, in partnership with state ophthalmology societies, has helped 34 state/territorial ophthalmology societies reject optometric scope-of-practice expansion into surgery.

To date in 2018, thanks to financial resources from the SSF, the Surgery by Surgeons campaign has netted patient safety and surgery standard preservation victories in the following battleground states:

- Florida
- Iowa
- Maryland
- Mississippi
- Nebraska
- North Carolina
- South Carolina
- Vermont
- Virginia

The 2018 battle is far from over, though. For example, California, Illinois, Massachusetts, and Pennsylvania are currently under assault. Furthermore, as of submission of this update in June 2018, the optometric surgery push had sprouted in six additional states.

Dollars from the SSF are critical in the state surgery campaigns. In each of these legislative battles, the benefits from SSF distributions are abundantly clear. The best lobbyists and public relations consultants are contracted as necessary. Additionally, media campaigns (including TV, radio, and social media) are launched to educate the voting public when needed. This helps to secure success in protecting patient safety by thwarting optometry's attempts to expand its scope of practice to include surgery privileges.

Each of these endeavors is very expensive, and no one state has the resources to wage one of these battles on its own. Ophthalmologists must join together and donate to the SSF to fight for patient safety when a state faces a scope battle over optometric surgery.

The Secretariat for State Affairs thanks the ASRS, the Macula Society, and the Retina Society for joining state ophthalmology societies in contributing to the SSF in 2017, and looks forward to their continued financial support. These ophthalmic complete the necessary SSF support structure for the creation and implementation of successful Surgery by Surgeons campaigns.

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: *Advocate for Your Profession & Your Patients*

Academy SSF contributions are used to support the infrastructure necessary in state legislative / regulatory battles and for public education. State PAC and OPHTHPAC contributions are necessary at the state and federal level, 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 Surgical Scope Fund, and your State Eye PAC. Please be part of the community advocating for your patients now.

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Surgical Scope Fund	OPHTHPAC® Fund	State EyePAC
To derail optometric surgical 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, lobbyists, PR and media campaigns	Campaign contributions, legislative education	Campaign contributions, legislative education
No funds may be used for campaign contributions or PACs.		
Contributions: Unlimited	Contributions: Limited to $5,000	Contribution limits vary based on state regulations.
Individual, practice, and organization		
Contributions are 100% confidential.	Contributions above $200 are on the public record.	Contributions are on the public record depending upon state statutes.

Retinal Malpractice Issues: The 30-Year OMIC Experience

George A Williams MD

Since its inception in 1987, the Ophthalmic Mutual Insurance Company (OMIC) has grown to provide medical liability insurance to over 5000 AAO member ophthalmologists. During this time, OMIC has closed over 4570 malpractice claims with a payment rate of 21%, resulting in more than $275 million in settlements, judgments, and related expenses. Over 820 of these claims are related to the management of vitreoretinal diseases, resulting in 114 payments averaging approximately $200,000.

OMIC considers every malpractice claim a learning opportunity to improve clinical care. A review of these claims often identifies recurring issues and trends. This presentation will discuss claims related to diagnostic errors, intravitreal injections, and retinopathy of prematurity (ROP).

Diagnostic error is the most common cause of a malpractice claim. In a recent study of diagnostic error claims from 2008 to 2014, OMIC found that diagnostic error related to retina was the most common cause, at 38% of all diagnostic errors. Of these, 79% were diagnostic error involving failure to diagnose retinal detachment. Expert review of 54 cases concluded that 50% of cases involving a comprehensive ophthalmologist (20 of 40) and 29% of those involving a retinal specialist (4 of 14) did not meet the standard of care. In cases with negative reviews, the most common cause of failure to meet the standard of care was the performance of the ophthalmologist. Other less frequent factors were systems issues, such as missed patient messages, and patient-related issues, such as noncompliance. Common and recurring ophthalmologist-related deficiencies were missing or poor documentation; diagnostic process deficiencies, including failure to perform scleral depression; examination deficiencies; and knowledge deficiencies, such as failure to recognize or consider known risk factors for retinal detachment. On review, 85% of patients had risk factors for retinal detachment.

Intravitreal injections are now the most commonly performed surgical procedure in ophthalmology. The AAO estimates that approximately 7 million injections were performed in 2017. As expected, medical malpractice claims related to intravitreal injections are increasing. OMIC analyzed 51 intravitreal injection claims from 1987-2016, with 36 of these claims since 2006 involving bevacizumab (26 cases), aflibercept (6 cases), and ranibizumab (2 cases). When compared to other, non–injection related claims, injection claims have a lower settlement rate (12%) and lower mean ($54,750 vs. $167,000) and median ($44,999 vs. $85,000) payment. These claims typically involved delayed diagnosis and treatment of postinjection endophthalmitis. Importantly, there have been no claims concerning the choice of drug, between bevacizumab, ranibizumab, and aflibercept. Recently, OMIC has become aware of claims concerning floaters due to silicone oil droplets associated with compounded bevacizumab. There are law offices actively soliciting such claims on the internet.

Claims related to ROP are infrequent, but they are associated with high severity of payments and high settlement rates. From 1987 to 2016, OMIC had 30 ROP claims, with a 50% settlement rate, a mean payment of $789,279, and a median payment of $500,000 (range: $26,666 to $3,375,000). Of the top 10 indemnity payments in the history of OMIC, 4 are related to ROP. Early OMIC experience with ROP claims demonstrated both systems-based and knowledge-based issues. There were cases where children were lost to follow-up and cases where ophthalmologists simply did not follow the standard of care. As a result, OMIC has instituted strict underwriting requirements for ophthalmologists involved in ROP care. Using the latest evidence-based medicine, these requirements are regularly updated by national ROP experts as screening and treatment patterns evolve. Optimal ROP care requires a team-based approach involving coordination and communication between the hospital, neonatologists, and ophthalmologists and their offices. OMIC has developed a program called the ROP Safety Net, with the goal of diminishing ROP-related blindness. The details of this program are available at no cost at omic.com.

MACRA and Beyond

William L Rich III MD

Prior to the passage of Medicare in 1965, 60% of the elderly lacked health insurance. To make Medicare more attractive to physicians, fees were determined by the "local, usual and customary" fee structure, and familiar local Blue Cross/Blue Shield carriers handled billing. What followed was explosive growth and cost to the federal system. Following is a listing of congressional legislation meant to control costs:

- Volume Performance Standards, 1993
- OBRA 1989, Resource Based Relative Value System
- BBA-Sustainable Growth Rate (SGR), 1997

All failed to reduce costs.

The SGR was developed to increase or decrease Medicare payments based on the level of Medicare spending compared to the GDP. Usually the SGR mandated cuts to physician fees that were obviated by congressional action. However, by 2012 the projected cuts had ballooned to 20%, and a new methodology was needed. Over the following years physicians aggressively lobbied for a new payment schedule. The problem is, physicians failed to follow the ancient proverb "Be careful what you ask for. You might just get it."

In 2015 Congress passed the Medicare Access and Chip Reauthorization Act (MACRA). This is without a doubt the most complex, irritating, confusing piece of health care legislation ever passed. Reading its 2398 pages made the Clinton Health Care Plan of 1100 pages feel like reading " Tommy the Train" to my grandsons!

The goal of MACRA was to move the Medicare fee-for-service (FFS) physician payment system to one based on "value rather than volume" (an insulting term to portray the physician's approach to health care delivery) and to pass the risk of federal payments downstream to docs. MACRA proposed two approaches for physicians to avoid penalties and earn small bonuses. One was a complex matrix that involved a revenue-neutral scoring of quality, costs, practice improvement, and use of technology (certified EHRs). Individual physician performance would increase or decrease payments by 4%, 5%, 7%, and then 9% over the next 4 years. To successfully navigate this complex program required practices to have instant access to a Medicare slide deck! The AAO IRIS Registry has enabled the profession to achieve the highest score of any other specialty.

The second approach was participation in risk-bearing alternative payment models, or APMs, which would reward Medicare physicians with bonuses of up to 5%. This would never cover the cost of the development and administration of the APM plan. For a successful APM there is an unattainable, impractical threshold of 75% of physician Medicare revenue. Consideration of this pathway is not an option for ophthalmologists. There are no viable alternative payment models available.

The emphasis on quality and cost is not going away, for either Medicare or commercial payers. So where does ophthalmic payment and delivery go from here?

There are other emerging trends that will affect the delivery of ophthalmic care. In Medicare, there has been an explosive growth in Medicare Advantage Plans (MA) stimulated by congressional passage in 2003 of the Medicare Modernization Act. MA participation rate has tripled since 2004, now accounting for 33% of all Medicare patients and predicted to hit 40% in the next couple of years. Five states already have rates of over 40%. Why the explosive participation rate? MA members usually have more benefits than those in FFS Medicare. For FFS patients there are three contracts to sign: Part B, a supplemental plan to cover the 20% noncovered Medicare charges, and a pharmacy plan. MA patients have only one contract. Patients are working longer and are comfortable changing health care plans to meet their individual needs. This option is offered by MA plans but not FFS Medicare.

Ophthalmologists' MA revenue is not subject to MACRA penalties or its administrative burden. The greater the percentage of MA patients in a physician practice, the less the financial impact of Medicare FFS penalties. This may be offset by MA policies of preauthorization of some drugs and surgical procedures.

In the commercial world the demand for the measurement of quality and costs will be a given. There will be more capitated contracts that carve out ophthalmic care similar to those in the late 80s. To manage these contracts that demand decreased cost and improved quality, the use of IRIS will be an invaluable tool.

There will be an acknowledged shortage of ophthalmologists in the face of the increasing demands to meet of needs patients with chronic ophthalmic diseases. The HHS HRSA agency estimates a 20% ophthalmic shortage by 2020. Fraher et al (*Annals of Surgery*, 2012) estimate a greater than 20% shortage by 2025. There is no possibility of increasing the number of residents beyond the current 418 to 425 per year, which won't even replace the loss of retiring ophthalmologists. How is the profession going to respond? The use of more technicians, paraprofessionals, and optometrists will help. The emerging use of artificial intelligence and machine learning to interpret images will free up physician time to devote more to direct medical and surgical care.

Our profession will continue to change. We must be innovative to meet the challenges ahead.

Efficient Workflow

Dennis P Han MD

Introduction

Efficient workflow is essential to optimizing productivity, patient and physician satisfaction, and staff morale. Efficiency can improve patient care by reducing rushing and confusion, creating time for safety measures, and decreasing the risk of medical error. It can also reduce costs to the practice, the patient, and the insurers. Efficient workflow does not mean working faster. Rather, it means working differently. Practicing efficiently is not usually taught in medical school, yet it is a key component to doing the most good for the most people. Prominent aspects of efficient workflow are discussed below.

Eliminating Process Wastes

Recognize the 8 wastes in health care delivery, remembered by the helpful mnemonic, "WISDOM TO change":

1. Waiting: A worker waits because information, space, or authority are missing.
2. Inventory: Too much or too little, or in the wrong place; examples are too many patients in a waiting room that are not being cared for, or unused and expired medications
3. Skills: Unutilized human resources
4. Defects: Doing things over because they weren't done right the first time
5. Overprocessing: Redundant steps, such as having to write things twice; excess paperwork; EHR inflexibilities
6. Motion: Excessive worker movement between tasks
7. Transportation: Equipment (or patient) kept too far from the workspace
8. Overproduction: Unnecessary effort spent on rapid throughput at one step when the bottleneck is somewhere else

Reducing Changeover

Making efficient use of physicians' time means concentrating their activity on the cognitive, examination, and procedural skills (described herein as "medical tasks") that create the opportunity for change in patient health. By eliminating changeover tasks (record-keeping, logistics, moving patients) from the physicians' workloads, we can maximize their impact on more patients in less time, while at the same time preserving face-to-face time with the patients. Physicians can thus transition quickly from one patient to the next and use all of their time improving patient health. The challenge is two-fold: (1) determining who performs those changeover tasks and (2) ensuring that the MD can give up control of these tasks.

The first challenge is met by reducing process waste and movement, thereby freeing up staff to assist with MD changeover. The second challenge, the issue of control, is largely under the physician's influence. Physicians must be willing to be flexible on points that do not affect patient outcomes. They must also recognize those points, which itself can be a challenge.

Multifunctionality of Staff and Space

"Multifunctionality of personnel" is the ability of individual staff members to change function when needed. It must be distinguished from "being cross-trained," whereby a person is capable of doing many tasks but might be assigned to a specific function, without the flexibility to change on a moment-by-moment basis. In contrast, true multifunctionality dynamically levels workloads by allowing staff to move to where they are needed, exactly when they are needed, and for the function for which they are needed. For instance, if one step is bogged down because too many patients are waiting, others can step in to assist with the bottleneck.

"Multifunctionality of clinic space" is the ability of patient-occupied space to serve multiple functions in the health-care process, often performed by multiple personnel, or even the same person whose function can change from moment to moment. Multifunctionality of space reduces excess motion by both patients and staff.

The goal of multifunctionality is to achieve true synchrony in clinic processes: neither physician nor patient wait for the other. This can be achieved by momentarily shifting technicians away from the tasks of reducing MD changeover time and toward bottlenecks elsewhere in the process, and then shifting back when the MD becomes the bottleneck.

A multifunctional clinic has the means by which a need for shifting resources is communicated. Most clinics lack this means and wallow in inefficiency as a result. A team leader, whiteboard (or EHR worklist that is instantly accessible to all team members), and signal lights can all work together to achieve this communication.

Multifunctionality can allow processes to work in parallel, rather than in series, to reduce effects of variation and dependency.

Implementation Essentials

- Start with a consistent staff and a consistent workspace—allowing gains to be consolidated and built upon from day to day and week to week.
- Follow some patients through the process to see what is actually happening; measure times at each step and waiting time in between.
- Use value stream mapping to identify bottlenecks and wastes.
- Engage your team in a group setting to share findings and gain input.
- Change one thing at a time. To encourage staff, emphasize the reversibility of any intervention; much pushback comes from the fear that anything new will be kept permanently, something that has likely been learned from previous experience.
- Expect unintended consequences of change, and mitigate if possible, weighing their effects against the benefit of the primary intervention. Allow some time for staff and MDs to adjust to the intervention and solve minor issues that arise.

Things to Try in Your Retina Clinic

- Try not moving patients between steps (such as screening, dilation, exam); use the staff time gained to assist with MD changeover. When increased staff time manifests itself as personnel standing around without anything to do while the MD is working, redirect their work toward helping the MD with changeover tasks.
- Keep all exam rooms and workstations within line of sight; identify a team leader (not the MD) to coordinate staff and MD activity from moment to moment.
- Use a whiteboard or other visual signals to indicate patient location and "who's next" for the MD to see. A whiteboard is particularly helpful when line of sight is not feasible, or if there are no visual signals at the exam rooms, such as signal lights or colored magnets. The whiteboard tends to be best introduced later in your transformation, after you have gained multifunctionality.
- Use the team leader to review schedules ahead of time and proactively head off problems.
- Eliminate the bottleneck effect of imaging: watch for unnecessary tests or subcomponents (eg, volume scans for certain patient types in which it is not needed, etc.).
- Establish protocols for dilation / imaging to eliminate interruptions of MD and patient flow.
- Construct schedule templates for rapid loading at the beginning of clinic with patients that require little workup, such as postop or injection-only patients.
- Remember the three essential characteristics desired when hiring staff—flexibility, capability, and motivation. Lacking any one of these attributes will inhibit your team member.
- Recognize your staff for their achievements in a concrete way. They are the core of your effort.

Selected Reading

1. Han DP, Suneja A. *Make Your Clinics Flow with Synchrony: A Practical and Innovative Guide for Physicians, Managers, and Staff*. Milwaukee: ASQ Quality Press; 2016. (ISBN 978-0-87389-923-9; available in hard copy or in electronic form at www.asq.org.)

Case Presentation

David Sarraf MD

NOTES

Case Presentation

K Bailey Freund MD

NOTES

Case Presentation

Lee M Jampol MD

NOTES

Case Presentation

Anita Agarwal MD

A 65-year-old woman with known history of adenocarcinoma of the lung Stage IIIB diagnosed in 2011 (5 years) presents complaining of no significant improvement in vision following cataract surgery. On further history she reports "shooting comets like flashes of light" in both eyes for the past 8 months. Blue colors appear faded with right eye, and the peripheral vision in the right eye has diminished.

She was treated with chemotherapy (cisplatin and etoposide) and radiation initially in 2012. Recurrence was treated with Lucanix vaccine, carboplatin, and paclitaxel (Taxol), followed by carboplatin/pemetrexed (Alimta). MTOR pathway mutation was found and treated with everolimus (Afinitor), topetecan, and radiation in 2014, followed by immunotherapy.

Her visual acuity was 20/32 O.D. and 20/20 O.S. Anterior segment exam was normal O.U. with centered posterior chamber IOLs. Fundus exam was mostly unremarkable except for a few focal areas of outer retinal changes in the inferior mid periphery of O.S. ERG showed reduced rod and cone function in the right eye and normal function in the left eye. Antiretinal antibodies were tested. Imaging findings, correlation with symptoms, medical history, and antiretinal antibodies will be discussed; and final diagnosis, established.

Case Presentation

Mystery Retina

William F. Mieler, MD

Case Summary

A 28-year-old female was referred for evaluation of a posterior segment mass lesion O.S. Vision was mildly impaired at 20/60 O.S. and IOP was mildly elevated in the mid-20s. A thorough ocular examination, echography, and a detailed past history helped to confirm the diagnosis

References

Will be provided at the presentation

Port Delivery Phase 2 LADDER AMD Study Results

Carl Regillo MD

Background

Neovascular AMD (nAMD) remains a leading cause of vision loss in adults over 50.[1] While the efficacy of anti-VEGF agents for nAMD is well established, treatment often requires frequent visits for monitoring and intravitreal injections that can pose a significant burden for patients, caregivers, and health care providers.[2] Real-world data suggest that many patients do not receive optimal treatment with intravitreal anti-VEGF injections for nAMD, and this undertreatment in clinical practice is associated with lower vision gains compared with gains achieved by patients in clinical trials.[3-5]

The port delivery system with ranibizumab (PDS) is an innovative drug delivery system that includes a refillable implant, surgically placed at the pars plana, which provides continuous intravitreal release of ranibizumab between clinic-based refill procedures.[6] Continuous delivery of ranibizumab via the PDS has the potential to reduce treatment burden and consequent undertreatment of nAMD patients in clinical practice. The safety and efficacy of the PDS in patients with nAMD is currently being evaluated in the Long-Acting Delivery of Ranibizumab (LADDER) trial.

Methods

LADDER (clinicaltrials.gov NCT02510794) is a Phase 2, randomized, interventional, active treatment–controlled, U.S.-based clinical trial. Eligible patients had nAMD diagnosed within 9 months of screening and a documented response to intravitreal anti-VEGF treatment. Patients were randomized in a 3:3:3:2 ratio to ranibizumab formulations of 10, 40, or 100 mg/mL, dosed using the PDS; or to monthly intravitreal ranibizumab 0.5-mg injections. The implant filled with ranibizumab was surgically placed in the pars plana at baseline. Eligibility for retreatment via an implant refill was assessed monthly based on protocol-defined criteria. Refill procedures were performed in the clinic using a novel refill needle capable of exchanging the implant contents with ranibizumab at full concentration. The primary endpoint is time in months to the first required refill according to protocol-defined refill criteria. Key secondary endpoints are change from baseline in BCVA and change from baseline in central foveal thickness on spectral domain OCT. Safety endpoints include incidence of ocular and non-ocular adverse events (AE) and AEs of special interest.

A total of 232 patients were enrolled in the LADDER trial, with 63, 63, and 63 patients in the 10-mg/mL, 40-mg/mL, and 100-mg/mL PDS arms, respectively, and 43 patients in the monthly intravitreal ranibizumab arm. The last patient enrolled completed 9 months of enrollment in May 2018. Demographics, baseline characteristics, and 9-month safety and efficacy data will be presented at AAO 2018 Retina Subspecialty Day.

Discussion

Real-world data suggest that many patients do not receive optimal treatment for nAMD, and this undertreatment in clinical practice is associated with lower visual acuity gains compared with randomized controlled clinical trials. Continuous delivery of ranibizumab via the PDS has the potential to solve the current unmet need of treatment burden and consequent undertreatment of nAMD patients in clinical practice. Results from the Phase 2 LADDER trial evaluating dosing and functional outcomes of continuous delivery of ranibizumab via the PDS will be presented at the meeting.

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Subthreshold Laser Therapies for Diabetic Macular Edemas: A Review of All Subthreshold Laser Technologies Available to Treat DME

Elias Reichel MD

I. Subthreshold laser includes all types of laser therapy that show no signs of damage to the examiner.

II. Significant Basic Science Work Supporting All Technologies
   A. Limited case series supporting clinical efficacy
   B. Most data on micropulse and endpoint management
   C. Micropulse supports foveal therapy for DME
   D. Endpoint management avoids fovea
   E. Microbubble disruption therapy avoids fovea

III. U.S. FDA-Approved Technologies
   A. Micropulse (3)
      1. Iridex (Micropulse)
      2. Quantel Laser (SubLiminal)
      3. Lumenis (SmartPulse)
   B. Continuous wave (1)
      1. Topcon (Endpoint Management)
   C. Microbubble disruption (1)
      1. Ellex (Retinal Rejuvenation Therapy = 2RT)

IV. Micropulse Laser
   A. Chops continuous-wave beam into an envelope of repetitive short pulses
   B. Duty cycle = % of time laser is "on" = 5%

V. Endpoint Management (Topcon)
   A. Arrhenius integral
   B. Describes the changes in temperature, in time and space in biologic tissues, in response to laser energy.
   C. Short pulse duration results in narrow therapeutic window.
   D. Biologic damage proportional to laser power

VI. Microbubble Photodisruption (Ellex)
   A. Selective targeting of individual retinal pigment epithelial (RPE) cells
   B. Microbubbles around melanosomes expand and result in intracellular damage.
   C. Individual RPE cell death
   D. Neighboring RPE cells migrate, divide, and produce new RPE cells.

VII. Subthreshold Laser Therapy: Practical Tips
   A. Choose correct Preset
   B. Confirm correct treatment mode; make sure you are not using conventional treatment mode.
   C. If using Micropulse, confirm 5% duty cycle.
   D. Be aware of landmarks and placement of treatment spots.

VIII. Several Different Subthreshold Technologies
   A. Significant clinical experience with Micropulse and Endpoint Management
   B. Subfoveal therapy possible with Micropulse only
   C. No clinical trials showing noninferiority or superiority to conventional laser with any of these subthreshold technologies

Micropulse Laser vs. Photodynamic Therapy for Central Serous Chorioretinopathy

Jay Chhablani MD

Introduction

Even if central serous chorioretinopathy (CSCR) is generally a self-limiting indication and only 20% of the cases present with persistent subretinal fluid lasting beyond 6 months, it still represents one of the most common retinal diseases following diabetic retinopathy, AMD, and vein occlusion. CSCR generally affects the young working-age population and in cases of chronic disease may result in severe visual loss caused by retinal pigment epithelium (RPE) atrophy or choroidal neovascularization.

General treatment approaches target treating the leak areas induced by hyperpermeable choroidal vessels, impaired choroidal vascular autoregulation, and dysfunction of the RPE barrier and pumping. A number of treatment options are available, including a number of oral medications with limited evidence, anti-VEGF with limited effectivity, and a larger range of threshold laser approaches. While threshold laser has been shown to be effective in reducing subretinal fluid, it bears the risk of iatrogenic damage. The more recently introduced microsecond pulsing laser eliminates this iatrogenic damage and still remains effective, as indicated in several comparative and noncomparative case series. Another treatment approach is photodynamic therapy (PDT), which has been shown to be effective (with good quality evidence).

Photodynamic Therapy

Evidence of the effectivity of PDT has been shown in a number of studies using various types of PDT, which are classified by fluence of laser and dosage of verteporfin (such as low-fluence PDT or half-dose PDT). In all types of PDT, verteporfin is usually infused over 8 or 10 minutes, followed by laser delivery at 689 nm at 10 or 15 minutes from the start of infusion in the area of the lesion targeted. The photoactivated verteporfin damages the vascular endothelium in the targeted area and leads to reduced choroidal perfusion, thereby decreasing choroidal hyperpermeability, a key factor in CSCR.

According to a 2014 meta-analysis, the probability of complete resolution of subretinal fluid when using half-dose PDT is statistically significant, with better results in terms of BCVA and reduction of subretinal fluid when compared to observation, and still significantly better than conventional slit lamp–based threshold laser. With the reduced dose or fluence/dose PDT, the risk of side effects is reduced but still present, with side effects including choroidal ischemia, neuroretinal thinning, choroidal neovascularization, or, very rarely, RPE tears. In addition, systemic complications have to be considered, including skin damage from excessive exposure to sunlight after treatment.

Microsecond Pulse Laser

A micropulse or microsecond pulse (MSP) laser has been introduced recently which uses a pulsed laser of either 810 or 577 nm, with 50-300 µs bursts within a 100-300 ms pulse duration envelope. This is limiting the thermal "injury" to the RPE below the photocoagulation threshold, where an up-and-down regulation of several gene expressions, including PEDF and VEGF and heat shock proteins, is triggered to initiate the treatment response. The MSP lasers generally result in an ophthalmoscopically invisible endpoint, complicating documentation and application in conventional laser systems. Using the navigated laser these shortcomings can be overcome, and a true confluency and a seamless documentation of the procedure can be ensured.

A broad range of publications provide analysis of the effectivity of the MSP laser for CSCR, with 60%-90% complete resolution of subretinal fluid, generally within 6 months, mostly using 5% DC, 125 µm, and 200 ms pulse durations (Scholz et al, 2017 review, reference #2). Side effects of the MSP laser have not been reported aside from 2 reports mentioning RPE changes at the location of laser impacts. However, these can be avoided with careful titration and the lowest effect fluence setting.

Comparison of Navigated MSP and Photodynamic Therapy

Few reports are available that compared PDT and MSP laser (Kretz et al; Scholz et al, 2016; Özmert et al; Roca, 2018; Ntokoma, 2018). All comparisons reached a better outcome with the MSP laser than with the usually either half-fluence or half-dose PDT; most of these studies showed a higher benefit with MSP that did not, however, reach statistically significant improvements. While Scholz et al achieved complete resolution in 36% with MSP, vs. 21% with PDT, Özmert et al reached 80% complete resolution with MSP, vs. 72% with PDT. Both of these studies used a 50% value of the threshold power for MSP laser and covered the whole area of thickening, whereas Ntokoma et al only used 30% of threshold power and covered only the leakage point. Despite the much lower power and area covered, a complete resolution of subretinal fluid could be detected in 60% of MSP patients, vs. 21% of PDT patients. This study also presented a statistically significantly better BCVA improvement. None of these comparison studies report on RPE changes after treatment or side effects from the treatment.

Conclusion

MSP laser seems to be at least as effective or potentially superior to PDT in the treatment of chronic CSCR. PDT is effective; however, it bears the risk of side effects, such as choroidal neovascularization, and is an invasive procedure, while MSP did not show any side effects. While both conventional MSP lasers and Navilas are laser equivalent, a much lower fluence resulted in a higher rate of complete resolution in concordance with a statistically better BCVA improvement as compared to PDT. This effect may be attributed to the navigation functions the system delivers. Additionally, the Navilas allows use without contact lens, definitely improving patient comfort and cooperation.

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Time-Elapsed Studies of the Retinal Capillaries in Clinical Vascular Disease Using Adaptive Optics: What Do They Tell Us?

Richard B Rosen MD

Histology provides exquisite details of microvascular anatomy, forever frozen in time. As with a single frame from a video, we can only guess what came before and what might have developed had the living tissue continued to function. Much of our description of capillary development and remodeling is based upon a "ransom note" made of images from different subjects, loosely strung together in a sequence that might appear logical, even if it is based upon imagination. To accurately describe the series of events we would need to be able to observe the microworld in situ.

The optical construction of the eye places many limits on our ability to observe such fine cellular details without disrupting its function. Spectral domain OCT has more recently given us amazing access to tissue details, drawing us ever deeper down the rabbit hole toward this shrouded microworld. At the limits of resolution, we are left wanting to see more.

Adaptive optics is a technique for breaking the resolution barrier, enabling observation of the tissue down to the cellular level. The technique was adopted from astronomy, where it is used to overcome the resolution limits imposed by atmospheric disturbance. Using a wavefront sensor with a deformable mirror that compensates for optical distortions, the optical system currently provides lateral resolution to the level of 2 microns. This is sufficient to resolve rod photoreceptors (2.5-micron diameter), as well as red blood cells in capillaries (5-8 microns) and internal structures of microaneurysm.

Serial imaging of vascular structures using adaptive optics offers a dynamic window onto microvascular histology. Structural remodeling over time can be observed without sacrificing the subject, opening the opportunity for studying clinical patients with a variety of vasculopathies.

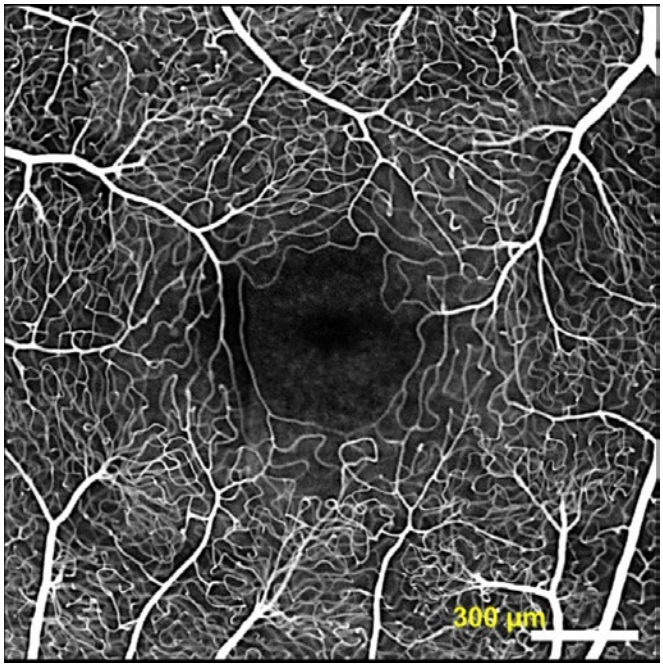

Figure 1. Adaptive optics scanning laser ophthalmoscopic fluorescein angiogram. Reprinted with permission from Pinhas A, Dubow M, Shah N, … Rosen RB. In vivo imaging of human retinal microvasculature using adaptive optics scanning light ophthalmoscope fluorescein angiography. *Biomed Opt Express*. 2013; 4(8): 1305-1317.

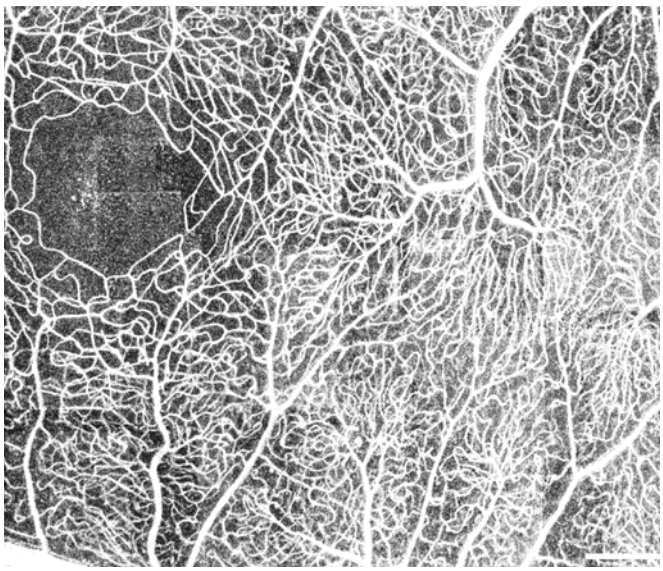

Figure 2. Motion contrast adaptive optics scanning laser ophthalmoscopic angiography. Reprinted with permission from Chui et al.

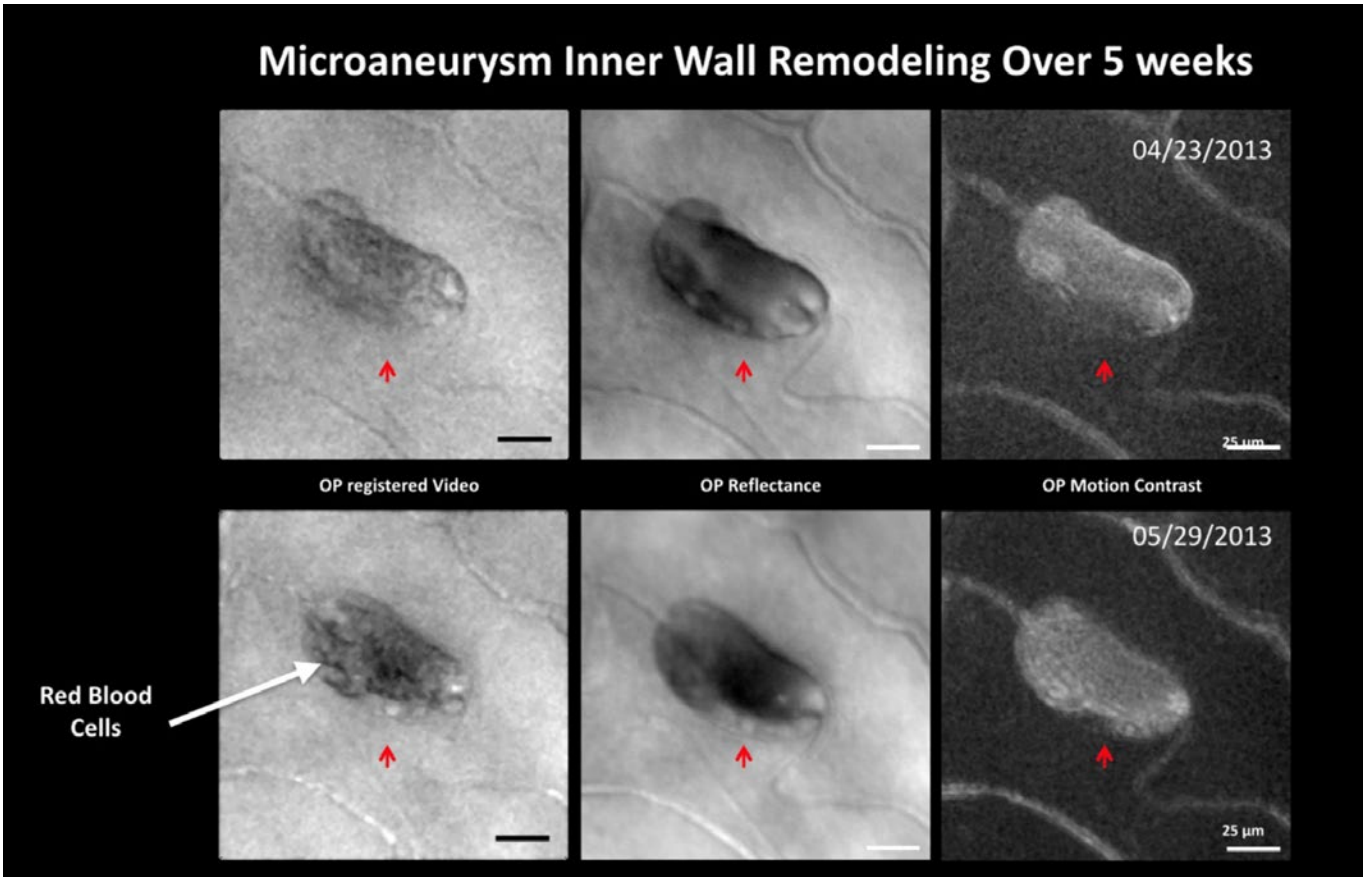

Figure 3. Reprinted with permission from Dubow M, Pinhas A, Shah N, … Rosen RB. Classification of human retinal microaneurysms using adaptive optics scanning light ophthalmoscope fluorescein angiography. *Invest Ophthalmol Vis Sci*. 2014; 55:1299-1309.

Capillary Remodeling in Conjunction With Glycosylated Hemoglobin Reduction

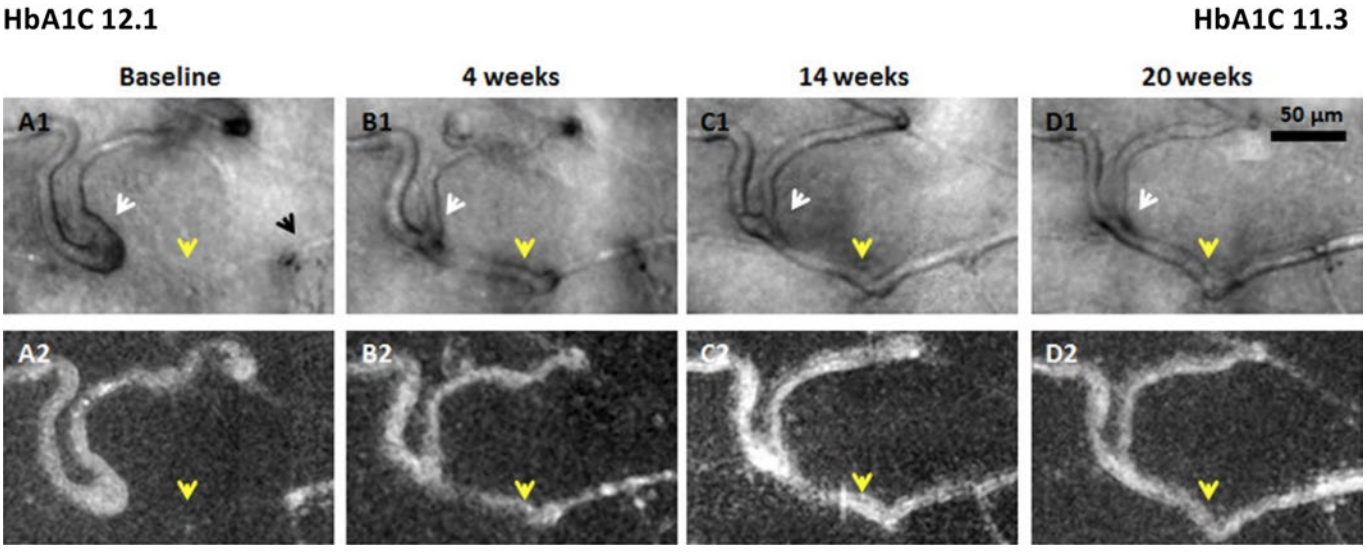

Figure 4. Recanalization of an occluded capillary. Top row shows adaptive optics scanning laser ophthalmoscopic structural images. Bottom row shows corresponding motion contrast perfusion maps. (A1) Black arrow indicates a capillary segment with an abrupt end. (A1–D1) White arrows indicate that as the neighboring capillary is recanalized and reperfused (gray arrows), vessel caliber and distortion decrease. HbA1C changes from 12.1 to 11.3; scale bar = 50 µm across. Reprinted with permission from Chui TY, Pinhas A, Gan A, … Rosen RB. Longitudinal imaging of microvascular remodeling in proliferative diabetic retinopathy using adaptive optics scanning light ophthalmoscopy. *Ophthalmic Physiol Opt*. 2016; 36(3):290-302 (fig. 5).

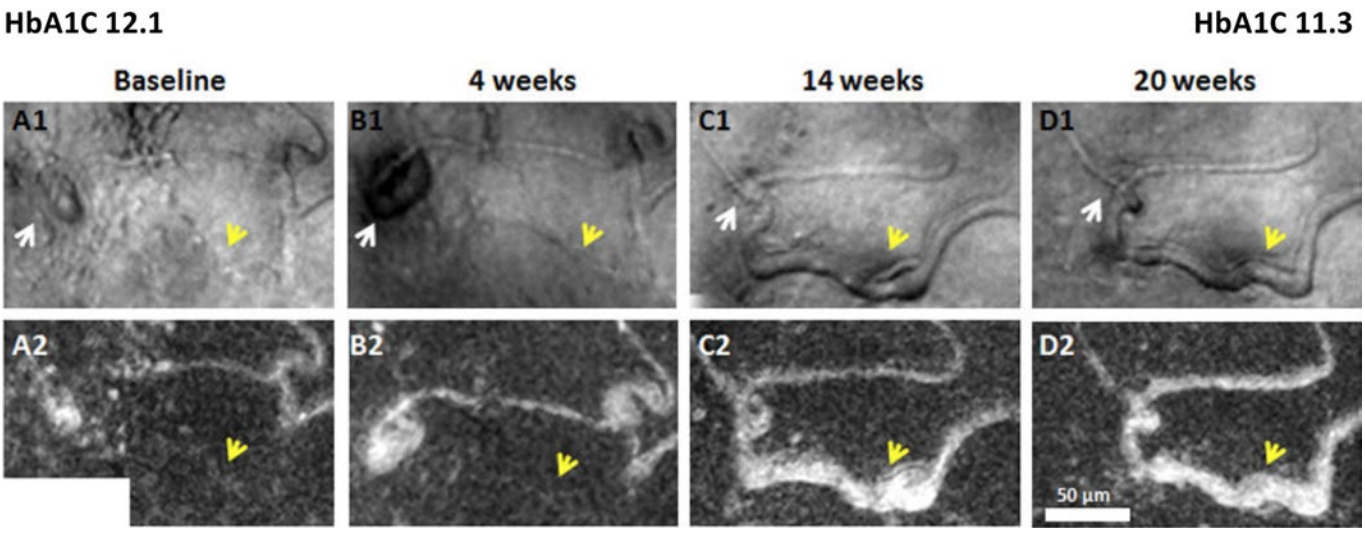

Figure 5. Capillary dilation after recanalization and reperfusion. Magnified region from Figure 4. Top row shows adaptive optics scanning laser ophthalmoscopic structural images. Bottom row shows corresponding motion contrast perfusion maps. A small microaneurysm (MA) can be seen along a dilated capillary (A1 & B1, white arrows). Regressed MA after capillary recanalization and reperfusion (C1 & D1, white arrows). Gray arrows indicate capillary dilation due to recanalization and reperfusion after the first two visits. Scale bar = 50 µm across. Reprinted with permission from Chui TY, Pinhas A, Gan A, … Rosen RB. Longitudinal imaging of microvascular remodeling in proliferative diabetic retinopathy using adaptive optics scanning light ophthalmoscopy. *Ophthalmic Physiol Opt*. 2016; 36(3):290-302 (fig. 6).

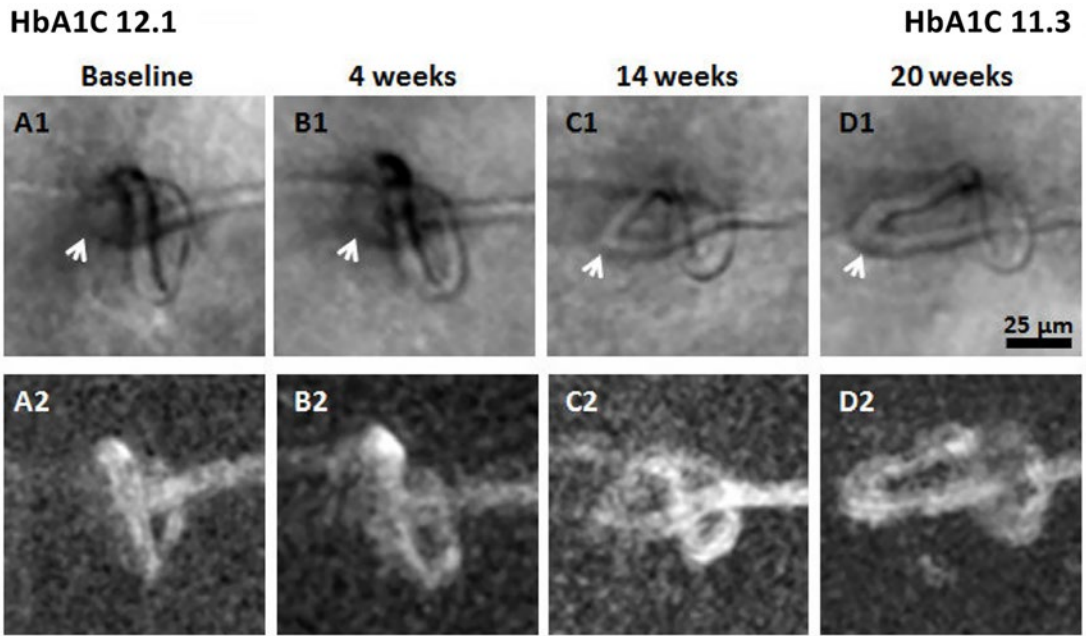

Figure 6. Formation of capillary bends. Top row shows adaptive optics scanning laser ophthalmoscopic structural images. Bottom row shows corresponding motion contrast perfusion maps. Arrows indicate the formation of capillary bends. Scale bar = 25 µm across. Reprinted with permission from Chui TY, Pinhas A, Gan A, … Rosen RB. Longitudinal imaging of microvascular remodeling in proliferative diabetic retinopathy using adaptive optics scanning light ophthalmoscopy. *Ophthalmic Physiol Opt*. 2016; 36(3):290-302 (fig. 7).

So What Do They Tell Us?

These images show us how microvascular changes such as capillary loops, curls, and microaneurysms respond to improvements in diabetic control with the capacity for reversing capillary closure and restoring blood flow. We can measure changes in vascular wall thickness over time in response to disease or therapeutic interventions.

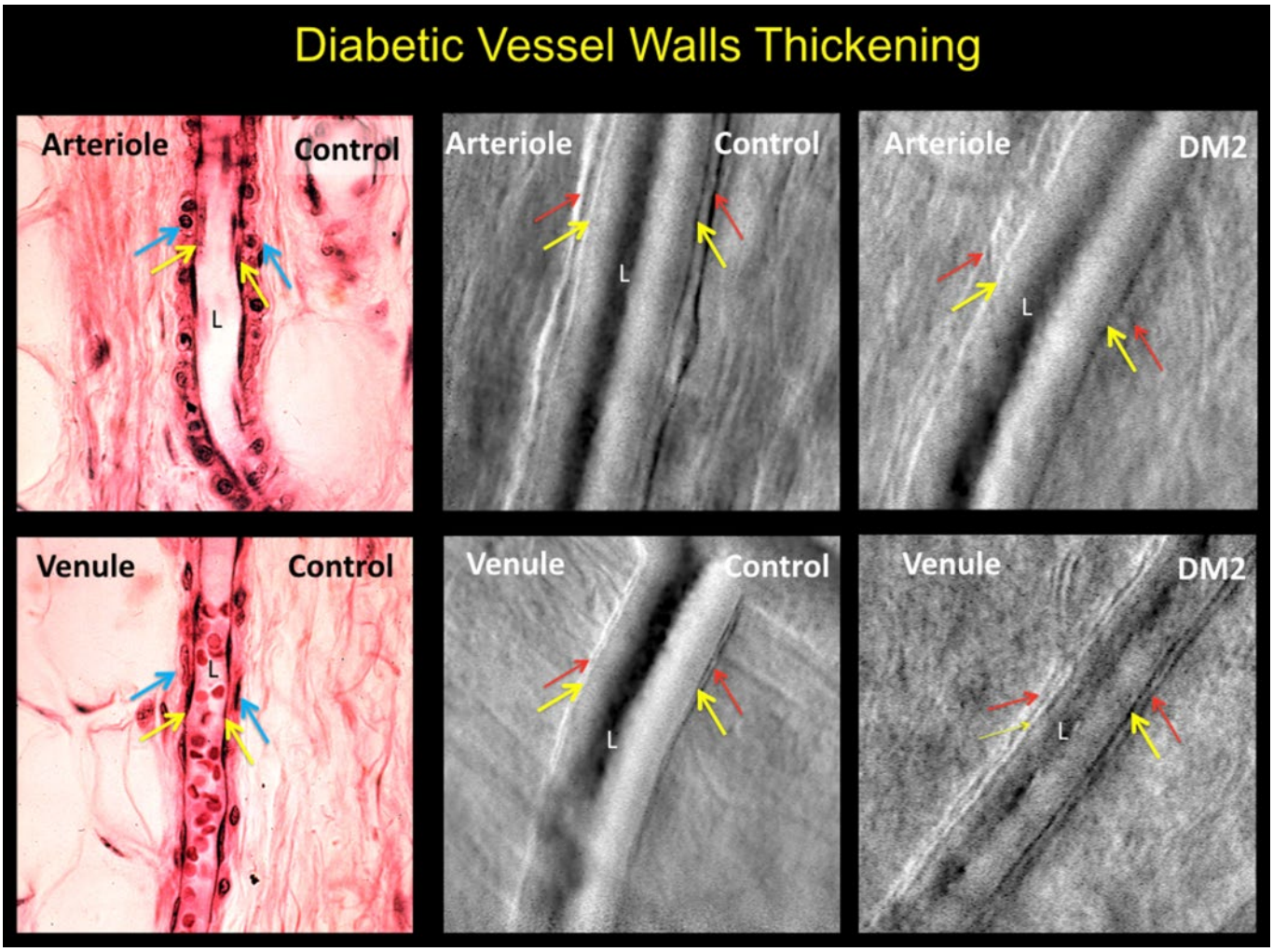

Figure 7. (Left) Histopathology examples. (Right) Offset pinhole adaptive optics scanning laser ophthalmoscopy.

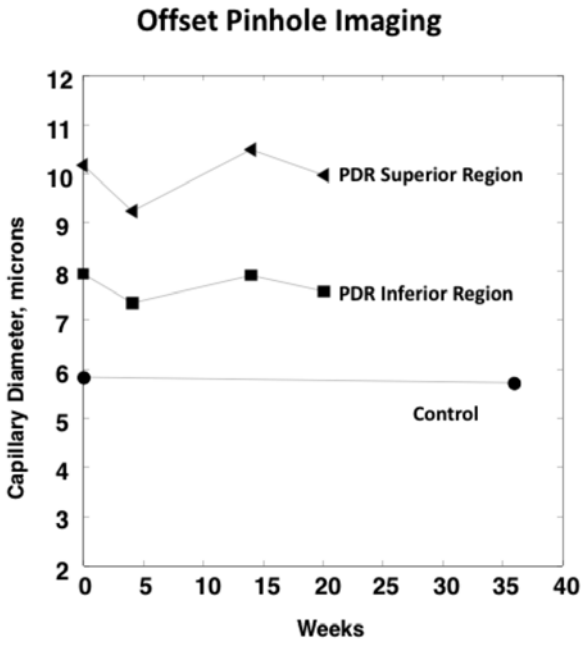

Figure 8. Comparable capillary wall measurements of diabetic vs. control eye.

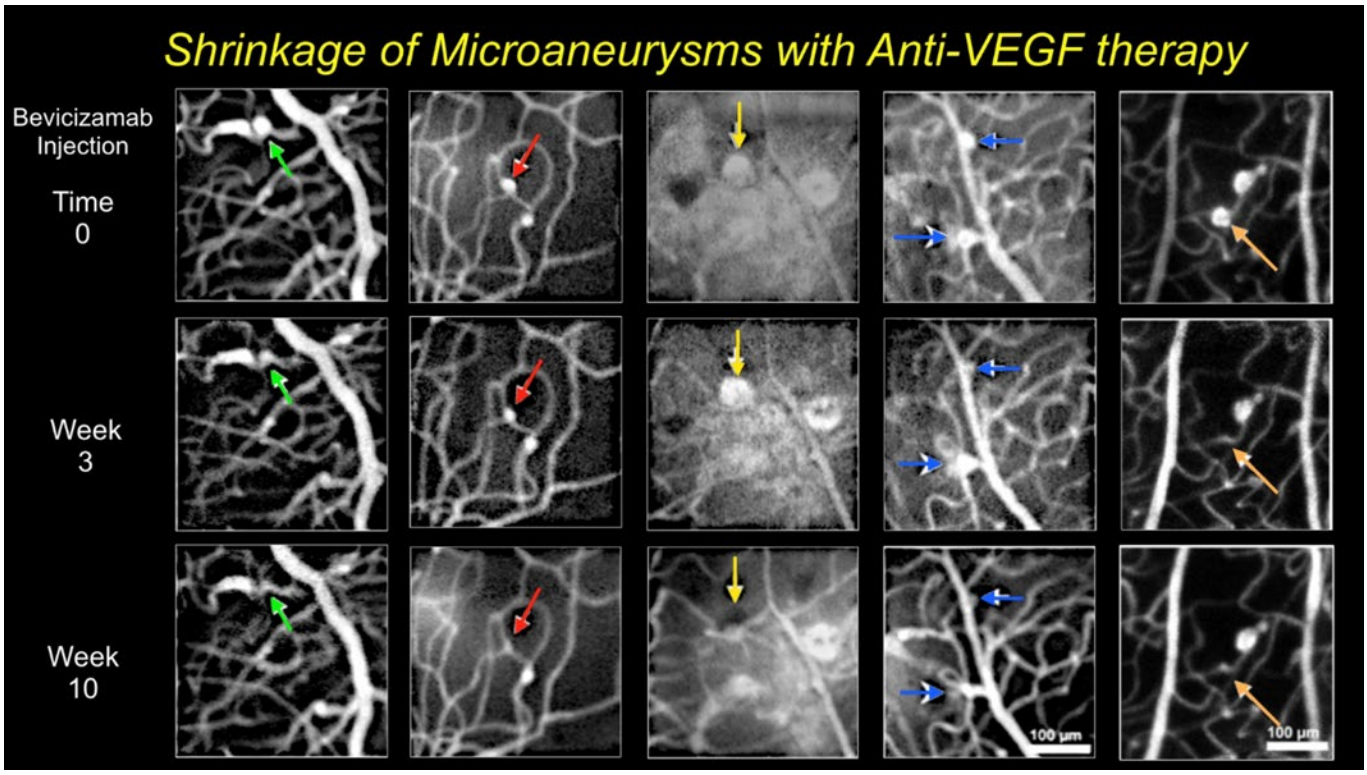

Figure 9. Clusters of microaneurysms in different regions of the macula of an eye with a central retinal vein occlusion. Following a single bevacizumab injection there is noticeable shrinkage of many of the microaneurysms over a period of 10 weeks. Reprinted with permission from Chui et al.

These images reveal the ability of pharmacotherapy to induce the absorption of microaneurysms with restoration of blood flow in capillaries. The potential to study vascular changes before clinical changes become apparent may have value for future pharmacotherapeutic trials.

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Optic Nerve Damage Due to Increased IOP Secondary to Dexamethasone Implant

Michael A Singer MD

Background and Objective

The dexamethasone (DEX) implant is known to cause temporary IOP spikes after implantation. The purpose of this study is to determine if IOP spikes after DEX implant cause significant thinning in the retinal nerve fiber layer (RNFL).

Study Design / Patients and Methods

306 charts were reviewed with 48 patients meeting inclusion criteria in this cross-sectional retrospective study. Inclusion criteria: IOP spike ≥ 22 mmHg up to 16 weeks after DEX implant, DEX implant in only 1 eye per patient, and OCT RNFL imaging of both eyes ≥ 3 months after IOP spike. The average RNFL thickness in the contralateral eye was used as the control. IRB approval was obtained.

Results

Overall, there was no statistically significant difference in mean RNFL thickness between the treated and the untreated eyes (80.4 ± 15.5 µm and 82.6 ± 15.8 µm, respectively; $P = .33$), regardless of treatment diagnosis, magnitude of IOP spike, or history of glaucoma.

Conclusions and Relevance

Temporary elevation of IOP after DEX implantation does not lead to a meaningful change in RNFL thickness.

Machine Interpretation of Fundus Photographs

Dale Webster PhD

NOTES

Vitrectomy and Uveitis

Janet Louise Davis MD

I. Vitrectomy for Diagnosis
  A. Infections: culture and polymerase chain reaction
    1. Endophthalmitis
      a. Chronic postoperative
      b. Endogenous
  B. Malignancies
    1. Intraocular lymphoma: clinical appearance
      a. Cytology
      b. Flow cytometry
      c. Gene rearrangements
    2. Vitreoretinal metastatic disease
      a. Histopathology
  C. Other conditions
    1. Amyloid: clinical appearance
      a. Formalin-fixed paraffin sections
        i. Congo red
        ii. Polarized microscopy for birefringence
        iii. Immunostaining for amyloid
    2. Chorioretinal lesions of uncertain etiology
      a. Chorioretinal biopsy

II. Vitrectomy for Treatment of Uveitis
  A. Infections
    1. Acute, severe endophthalmitis
    2. Chronic postoperative
    3. Necrotizing viral retinitis (NHR), to prevent retinal detachment
  B. Noninfectious intermediate uveitis
    1. Pars planitis
      a. Stepladder approach
      b. Combination with medical therapy
      c. Monitoring for efficacy
  C. Other noninfectious uveitis
  D. Review of therapeutic vitrectomy before and since 2005
    1. Low levels of medical evidence; retrospective with limitations in design
    2. Poor adherence to standard nomenclature and outcomes

III. Vitrectomy for Vision
  A. Nonclearing vitreous opacities
    1. Healed infections: toxoplasmosis
    2. Fuchs uveitis syndrome
  B. Combined with cataract surgery
  C. Macular disease: cystoid macular edema and epiretinal membrane

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Drug-Induced Uveitis

Emmett T Cunningham Jr MD PhD MPH, prepared in collaboration with Meena Moorthy and Ramana S Moorthy MD

I. Introduction

A. Although uncommon, drug-induced uveitis is well recognized and associated with an increasing number of pharmacotherapeutics.

B. Drug-induced uveitis is easily overlooked. A detailed medical / drug history is essential.

C. While the mechanisms of drug-induced uveitis are largely unknown, agents known to act through direct modulation of the immune system are believed to induce uveitis as an equally direct, albeit unwanted, consequence of that immunomodulation (eg, TNF inhibitors, checkpoint inhibitors).

D. Naranjo et al have proposed a list of 10 criteria to be used to determine the level of evidence supporting the supposition that a given agenda can cause uveitis.[1]

II. Systemic Agents Definitely Associated With Uveitis

Resolve with discontinuation and treatment with corticosteroids.

A. Immune checkpoint inhibitors

1. Ipilimumab (anti-CTLA-4; Yervoy), pembrolizumab (Keytruda), and nivolumab (Opdivo); both anti-PD-1

a. One percent of patients develop uveitis.

b. Over 50 cases to date

c. Over 90% treated for metastatic malignant melanoma.

d. Sixty percent have other non-ocular autoimmune complications. Anterior uveitis is most common; uncommon, orbital inflammation. Most bilateral.

2. Atezolizumab, avelumab, and durvalumab anti-PD-L1 (no reported cases of uveitis yet)

B. MEK inhibitor (trametinib [Mekinist]) and BRAF inhibitors (vemurafenib [Zelboraf] and dabrafenib [Tafinlar])

1. For metastatic melanoma

2. Anterior, intermediate, or panuveitis

3. Most bilateral

C. Cidofovir

1. For cytomegalovirus retinitis

2. Nongranulomatous anterior uveitis and hypotony

3. Hypotony may persist.

D. Rifabutin

1. As prophylaxis for Mycobacterium avium complex (MAC)

2. Anterior ± hypopyon.

E. Sulfonamides

1. Antibiotics / anticonvulsants / diuretics

2. Nongranulomatous anterior uveitis

F. Bisphosphonates

1. For osteoporosis

2. Uveitis, scleritis, episcleritis, orbital inflammation

3. Implicated agents include pamidronate (Aredia), etidronate (Didronel), risedronate (Actonel and Atelvia), alendronate (Fosamax and Binosto), and zoledronic acid (Reclast). Pamidronate most common.

G. Tumor necrosis factor inhibitors

1. Especially etanercept (Enbrel), but also infliximab (Remicade) and adalimumab (Humira)

2. May be granulomatous

III. Intravitreal Agents

A. Anti-VEGF agents: < 1%

B. Cidofovir

IV. Topical Agents

A. Metipranolol

1. Nonselective beta-blocker

2. Granulomatous anterior uveitis

B. Brimonidine

1. Selective alpha2-adrenergic agonist

2. Granulomatous anterior uveitis

C. Prostaglandin agonists: latanoprost, travoprost, bimatoprost

V. Vaccines
   A. Human papillomavirus vaccine (Gardasil)
      1. Anterior ± papillitis
      2. Vogt-Koyanagi-Harada–like
      3. Ampiginous
   B. BCG
   C. Varicella virus vaccine
   D. Hepatitis B vaccine
   E. Hepatitis A vaccine

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Polymerase Chain Reaction

Russell N Van Gelder MD PhD

Introduction

Since its description 30 years ago, the polymerase chain reaction (PCR) has continued to facilitate the analysis of nucleic acids from biologic samples. As applied to ocular infectious disease, this technique allows rapid amplification of infinitesimal quantities of nucleic acid into analytic amounts, allowing for the rapid detection and identification of potential pathogen DNA and RNA within a sample.

Types of PCR

PCR may be performed on DNA or RNA (via reverse transcriptase, also known as RT-PCR). PCR may be performed in monoplex or in multiplex (ie, several primer sets analyzed simultaneously). PCR may be performed qualitatively or quantitatively (ie, qPCR). Detection of products may be by electrophoresis or by melt-curve analysis.

Applications to Ophthalmic Infectious Disease

The traditional application of PCR to ocular inflammatory disease has been in detection of herpes family viruses in acute retinal necrosis, progressive outer retinal necrosis, and cytomegalovirus (CMV) retinitis. The technique remains highly useful in these diseases, as well as in cases of ocular toxoplasmosis. More recently, clinical use of 16S (bacterial) and 18S / 28S / ITS conserved sequence PCR has allowed for the detection and rapid characterization of bacteria and fungi from ocular samples, facilitating diagnosis of endogenous endophthalmitis. Several groups have recently combined PCR techniques into a panel format capable of evaluating for many diseases simultaneously.

Frontiers of Molecular Diagnostics for Ocular Inflammatory Disease

In the past several years, DNA sequencing costs have dropped dramatically, allowing application of "next-generation" sequencing technologies to ocular infectious disease. Application to bacterial endophthalmitis, for example, has shown potential for rapid identification of pathogens as well as molecular identification of antibiotic susceptibility. Such techniques will likely supplant traditional PCR in the foreseeable future.

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Three Pearls for Uveitis

Narsing A Rao MD

Overview: Diagnosis of uveitis entities one should not miss

1. Do not miss infectious etiology.
2. Avoid missing diagnosis of uveitis associated with life-threatening systemic disease.
3. Do vitreous and/or retinochoroidal biopsy when faced with unexplained uveitis etiology.

I. Infectious Uveitis

A. Toxoplasmic retinochoroiditis

1. Immunocompetent
2. Immunocompromised

B. *Treponema pallidum* (syphilis) uveitis; anterior, intermediate, and posterior uveitis

1. Immunocompetent
2. Immunocompromised

C. Tuberculous uveitis; anterior, intermediate, posterior, and pan uveitis

1. Patient from tuberculosis endemic country; serpiginous, like choroiditis
2. Patients of nontuberculosis endemic countries; primarily chorioretinitis

D. Herpetic retinitis (acute retinal necrosis)

1. Immunocompetent individual: vitritis, retinitis, choroiditis, vasculitis, disc swelling
2. Immunocompromised individual: progressive outer retinal necrosis (PORN), minimum or no vitritis, rapidly progressing retinitis

E. Tailored investigations to support clinical diagnosis of infectious uveitis

1. Serology tests: toxoplasmosis IgG and IgM, rapid plasma reagin (RPR) test, Venereal Disease Research Laboratory (VDRL) test, specific treponemal antibody test (such as FTA), gamma interferon release assay for mycobacterium tuberculosis, HSV, VZV, CMV, IgG and IgM tests
2. PPD (purified protein derivative) Mantoux test: 0.1 mL of liquid containing 5 tuberculum units of intradermal injection, read 48-72 hours after the injection
3. Ocular fluid examination to detect DNA of infectious agent by polymerase chain reaction (PCR), culture and histology
4. Rarely, retinochoroidal biopsy is required.

II. Uveitis Associated With Life-Threatening Systemic Disease

A. Demyelinating disease; multiple sclerosis (MS)

B. Infections; syphilis, tuberculosis, toxoplasmosis in immunocompromised, Whipple disease

C. Vasculitides, including Behçet disease

D. Systemic and other inflammatory diseases; Vogt-Koyanagi-Harada (VKH) disease, sarcoidosis, multifocal placoid pigment epitheliopathy

E. Neoplastic; primary intraocular lymphoma

F. Among the above entities, first consider entities such as syphilis, VKH, MS, and primary intraocular lymphoma (primary vitreoretinal lymphoma).

III. Unexplained Cause of Uveitis With Progressive Loss of Vision

Vitreous biopsy, particularly retinochoroidal biopsy, is rarely required for diagnosis of uveitis entities. In most instances, diagnosis of the entity is made on basis of clinical exam and supported by laboratory investigations. In patients with compromised immune status and in patients with masquerade entities such as primary vitreoretinal and primary uveal lymphomas, vitreous and rarely retinal and choroidal biopsy may be required to establish tissue diagnosis for therapeutic interventions. It is important to talk to a pathologist prior to vitreous, retinochoroidal, or uveal biopsy for proper cytological, immunohistochemical, flow cytometry, PCR for immunoglobulins gene rearrangements, and cytokine levels (IL10, IL6 ratio) determination.

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Uveitis Case Panel Discussion

Panel Moderator: Sunil K Srivastava MD

Panelists: Nisha Acharya MD, Hatice N Sen MD, Albert T Vitale MD, Steven Yeh MD

NOTES

My Coolest Surgical Video

Internal Limiting Membrane Repositioning for Macular Hole Due to Rupture of Retinal Macroaneurysm

Yuki Morizane MD

Surgical Pupilloplasty for Secondary Angle Closure Glaucoma Induced by Silicon Oil Tamponade

Priya Narang MS

Use of Intraoperative OCT in Ensuring Optimal Array Retina Contact During Argus II Implantation Surgery

Young Hee Yoon MD

What to do When Your Fluid/Air Exchange Doesn't Work?

Gustavo Matias Huning MD

Foldable Subretinal Scaffold with Stem Cell Derived RPE in GA

Amir H Kashani MD PhD

Anti-VEGF for ROP: What Drug and What Dose?

Robert L Avery MD

I. Benefits of Anti-VEGF for ROP
   A. BEAT-ROP
   B. Lack of registration trials for ROP
II. Anti-VEGF Agents for ROP
   A. Pegaptanib
   B. Bevacizumab
   C. Ranibizumab
   D. Aflibercept
III. Pharmacokinetic Differences
   A. Systemic exposure in adults
   B. Systemic exposure in ROP
IV. Are Systemic Anti-VEGF Levels Significant?
   A. Could they affect retinal neovascularization?
      1. ROP levels much higher than in adults
      2. Concentrations that could affect neovascularization in proliferative diabetic retinopathy
   B. Fellow eye effects
   C. Concern over neurodevelopment
V. Optimum Anti-VEGF Dose
   A. Lower dosing
      1. Animal studies
         a. Equally effective for retinal neovascularization
         b. Less inhibition of vasculogenesis and revascularization
      2. Human studies
VI. Duration of Effect
   A. Is there a difference in durability of effect between the agents?
   B. Why might bevacizumab theoretically last longer than ranibizumab?
VII. Future Directions

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.
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Clinical Features and Management of "Crunch" Detachments Following Anti-VEGF Treatment for ROP

Antonio Capone Jr MD

I. Background
   A. Pathogenesis of ROP as a response to ischemia
   B. Role of VEGF and other cytokines
II. Anti-VEGF Agents
III. Study Cohort
IV. Findings
   A. Timing of progression to tractional retinal detachment (TRD) following anti-VEGF treatment
   B. TRD configurations unique to acute ROP treated with anti-VEGF agents
      1. Circumferential contraction
      2. Prepapillary contraction
   C. Associated features: bilateral symmetry in prepapillary contraction
V. Surgical Management
   A. Circumferential contraction in acute ROP following anti-VEGF treatment
   B. Prepapillary contraction in acute ROP following anti-VEGF treatment
   C. Focal hyaloidal contraction
      1. In children
      2. In adults
   D. Diffuse hyaloidal
      1. In children
      2. In adults
VI. Long-term Issues With Persistent Avascular Retina
   A. Following spontaneous regression of acute ROP
   B. Following anti-VEGF treatment of acute ROP
VII. Conclusions

Selected Readings

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Repair and Regeneration Wnt Signaling: What and Why

Michael Trese MD

Many inherited and acquired retinal vascular diseases have negative effects on the retina and eye because of vascular leakage and capillary dropout. To date leakage has been treated by therapies that target VEGF blockade, and for capillary dropout no purposeful therapy has been available.

Wnt signaling is a transduction pathway made of multiple proteins that is triggered by a Norrin protein binding to the Fz4 cell surface receptor. In an infant this Norrin-driven Wnt signaling results in normal CNS, auditory, and retinal vascular structure, creating good vascular tight junctions and appropriate retinal capillaries.

It was thought that this Norrin-driven Wnt signaling was not possible in adult retinal endothelial cells—that only Wnt 3a, 7a, and 10 could bind to the Fz4 cell surface receptor and trigger Wnt-driven Wnt signaling that has been associated with pathologic conditions, such as cancer, rheumatoid arthritis, and other pathologic vascular conditions. However, we have demonstrated in human adult retinal endothelial cell tissue culture and in animal models that we can produce Norrin-driven Wnt signaling, inducing rapid repair of retinal vascular tight junctions and for the first time in animal models a purposeful regeneration of appropriate retinal capillaries to treat capillary drop out.

Norrin-driven Wnt signaling promises to provide a new therapeutic path for retinal vascular leakage diseases, reforming tight junctions and for the first time purposeful capillary regeneration for both inherited and acquired retinal vascular diseases.

Anti-VEGF Treatment for ROP: Clinical Trials and Phenotypic Differences Worldwide

Mary Elizabeth Hartnett MD

I. Rationale for Vascular Endothelial Growth Factor (VEGF) Involved in Severe ROP

A. Important in adult diabetic retinopathy, neovascular AMD

B. Preclinical testing of anti-VEGF in adult disease used oxygen-induced retinopathy models that share characteristics with human ROP (stage 3 – intravitreal neovascularization; plus disease – arteriolar tortuosity and venous dilation)

II. Caution Regarding Use of Anti-VEGF in ROP

A. VEGF is important in human retinal vascular development.

B. VEGF is neuroprotective.

Experimental evidence that optimal anti-VEGF dose thins outer nuclear layer and causes release of neuroprotective factors from Müller cells

C. VEGF necessary to support newly developed retinal capillaries under oxygen stresses similar to human ROP. Experimental intravitreal anti-VEGF:

1. Injures newly developed retinal capillaries
2. Leads to compensatory increases in VEGF
3. Results in recurrent intravitreal neovascularization

D. Anti-VEGF agents enter the bloodstream of preterm infant eyes and reduce serum VEGF; may adversely affect developing organs of premature infant.

III. Clinical Trials Testing Agents, Doses, and Safety

A. BEAT-ROP study

1. Bevacizumab vs. laser for zone 1 or posterior zone 2 ROP with stage 3 and plus disease
2. 0.025 mL of 25 mg/mL (0.625-mg bevacizumab) reduced recurrence of severe ROP to 4% in bevacizumab-treated compared to laser-treated eyes (22%) by 54 weeks postmenstrual age.
   a. Recurrent severe ROP can occur later than 54 weeks (one report up to 3 years after treatment).
   b. Follow-up study of 11 patients (22 eyes) treated with bevacizumab vs. laser in 17 patients (32 eyes) from BEAT-ROP had less severe myopia at 22.4 months (–2.4 D vs. –5.3 D) with recurrent severe ROP in 8.3% (8%-26%) on average 16.2 weeks after treatment.

B. ROP1 study (Pediatric Eye Disease Investigator Group [PEDIG])

1. De-escalating dose study of bevacizumab in treatment-naive type 1 ROP in 1 or both eyes found reduced severe ROP at 1 month with 1/20th the dose (0.031 mg).
2. Success at 4 weeks in 55/58 infants (from 61 enrolled)
3. By 6 months, 25 of 61 study eyes received treatment: 3 for failure within 4 weeks, 11 for recurrence after 4 weeks, and 11 for persistent avascular retina.
4. All 10 eyes given 0.031-mg dose had success with reattached retinas without retreatment for early failure or late recurrence at 6 months, and 3 of the 0.031-mg dose group were treated for persistent avascular retina.
5. At > 6 months, stage 4A ROP developed in 1 eye, stage 4B in 1 eye, and stage 5 in 2 eyes from different infants. Six infants died from pre-existing conditions prior to enrollment.

C. CARE ROP study

Ranibizumab has less systemic absorption and shorter half-life than bevacizumab; ranibizumab at 2 doses (0.12 mg or 0.2 mg) was successful in controlling acute ROP, defined as not requiring rescue treatment at 24 weeks.

IV. Phenotypic Differences Worldwide

A. Peripheral severe ROP vs. aggressive posterior ROP

B. ROP in older babies

1. Oxygen-induced retinopathy
2. Prenatal nutrition and maternal/fetal effects (eg, pre-eclampsia)
3. Perinatal resources (staff, ventilators, regulation of oxygen)

C. Diagnostic ability

D. Genetic factors

E. Risk of systemic anti-VEGF varies by infant blood volume and development, which differs.

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Pediatric Retina Panel

Panel Moderator: Philip J Ferrone MD

Panelists: Audina M Berrocal MD, Cagri G Besirli MD, Kimberly A Drenser MD PhD, G Baker Hubbard MD

NOTES

Late Breaking Developments, Part I

Relentless Long-term Progression of Hydroxychloroquine Retinopathy
Michael F Marmor MD

Visual Function after Anti-VEGF Therapy for Macular Edema due to Central Retinal Vein Occlusion: SCORE2 Trial Results
Ingrid U Scott MD MPH

24-month Evaluation of Fluocinolone Acetonide Intravitreal Insert Treatment for Non-Infectious Posterior Uveitis
Quan Dong Nguyen MD

Sub-Threshold Nanosecond Laser Intervention in Age-Related Macular Degeneration: The LEAD Randomized Controlled Clinical Trial
Robyn H Guymer MBBS PhD

First Results of Photovoltaic Vision Restauration in Atrophic Dry Age-related Macular Degeneration
Jose A Sahel MD

New Low-cost Intravitreal Biosimilars (Bevacizumab and Ranibizumab) for Retinal Vascular Diseases
Alay S Banker MD

First-time Results of Clinical Trials

26 Week Results of the Phase I Study to Evaluate Safety & Tolerability of RGX-314 Gene Therapy in AMD Subjects

Jeffrey S Heier MD

Safety and Efficacy of Abicipar in Patients with Neovascular Age-related Macular Degeneration

Rahul Khurana MD

Simultaneous Inhibition of VEGF and Ang-2 with Faricimab in Neovascular AMD: STAIRWAY Phase 2 Results

Arshad M Khanani MD

Brimonidine DDS Safety and Efficacy in Patients with Geographic Atrophy Secondary to Age-related Macular Degeneration

William R Freeman MD

Clinical Utility of OCT Angiography

Jay S Duker MD and Malvika Arya BS

Introduction

Optical coherence tomography angiography (OCT-A) is a non-invasive, depth-resolved imaging modality. A decorrelation signal is measured between successive OCT B-scans at the same retinal cross-section to detect areas of motion due to erythrocyte flow through blood vessels. This generates a volumetric cube scan of the retina, coupling structural and angiographic data.[1] The volume set can be scrolled through from the inner retina down to the choroid, or it can be segmented into individual vascular plexuses. Each OCT-A scan consists of 245-500 OCT B-scan locations, depending on the device and scan pattern.

Current commercially available OCT-A scan patterns range in size from 3x3 mm to 12x12 mm and 15x9 mm. However, B-scan positions spread out as the retinal field of view increases, thereby reducing sampling density and image resolution with larger scan areas.[1]

Compared to fluorescein angiography (FA), OCT-A is less invasive, faster, and has higher resolution. However, OCT-A is susceptible to artifacts, such as motion and projection artifacts, that make it difficult to interpret some images.[2] Projection artifact removal algorithms and techniques to reduce motion artifacts continue to be improved upon.[3,4] Until more recently, a limitation of OCT-A was a limited peripheral field of view. However, with the development of swept source technology, which allows for faster scanning speeds, OCT-A images may now be montaged within device manufacturer software to generate a field of view comparable to that of standard FA.

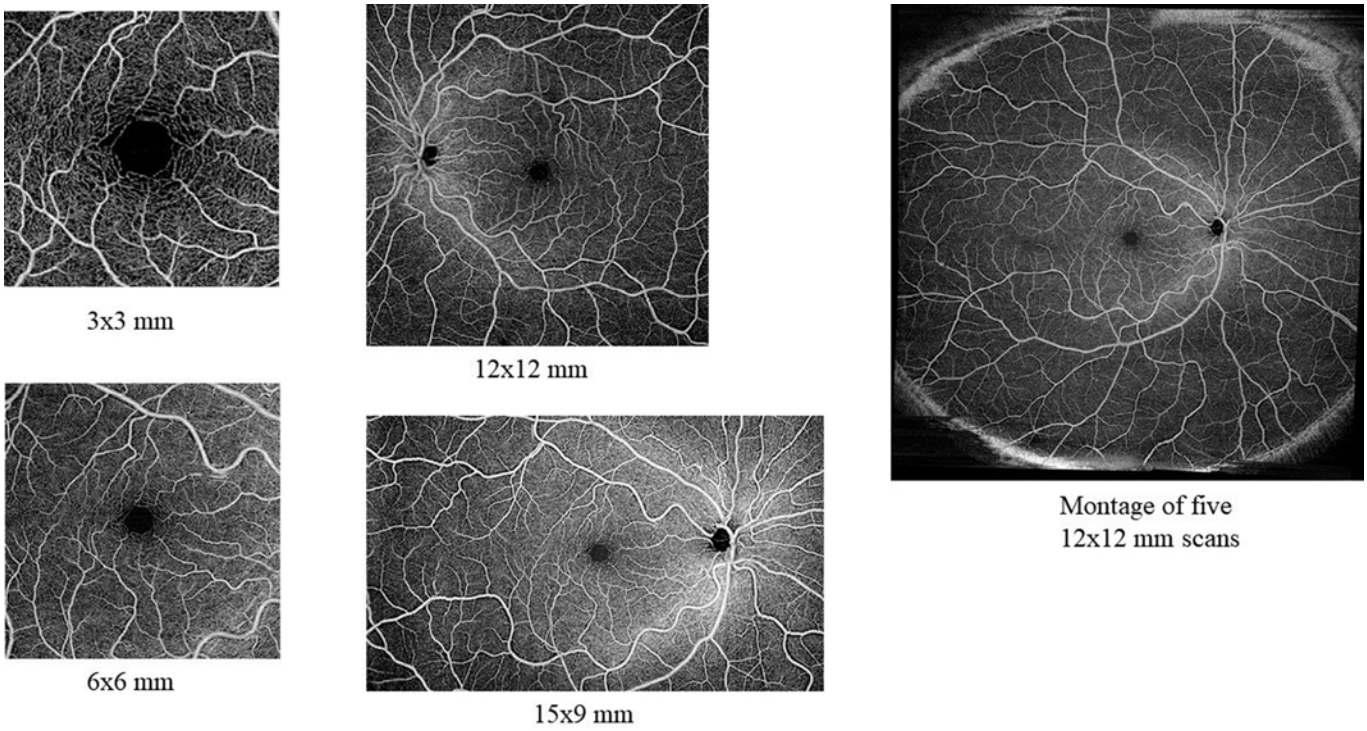

Figure 1. Various OCT-A scan patterns.

Clinical Utility of OCT-A

Wet AMD—Diagnosis of CNV

OCT-A has demonstrated particular utility in neovascular (wet) AMD. It is very useful for the diagnosis of choroidal neovascularization (CNV) and is comparable, or even superior, to FA in this regard.[5,6] CNV is detected in 2 ways

1. Visualization of flow in the outer retina, a region normally devoid of vasculature and/or
2. Abnormal morphology of vasculature in areas normally featuring blood vessels (eg, the choroid)

Type 1 and 2 CNV can be differentiated by segmenting either below or above the retinal pigment epithelium, respectively. Additionally, the corresponding OCT B-scans can assess for the presence of subretinal fluid.

Dry AMD—Diagnosis of Nonexudative CNV

OCT-A is excellent for visualizing nonexudative CNV in eyes that appear to have only dry AMD clinically.[7] Such findings may guide treatment decisions and frequency of patient follow-up.

Left: Structural OCT scans demonstrating drusen and a flat irregular retinal pigment epithelial detachment (RPED) without subretinal fluid

Right: SD-OCTA scan showing presence of quiescent, treatment-naïve CNV with abnormal vessel morphology

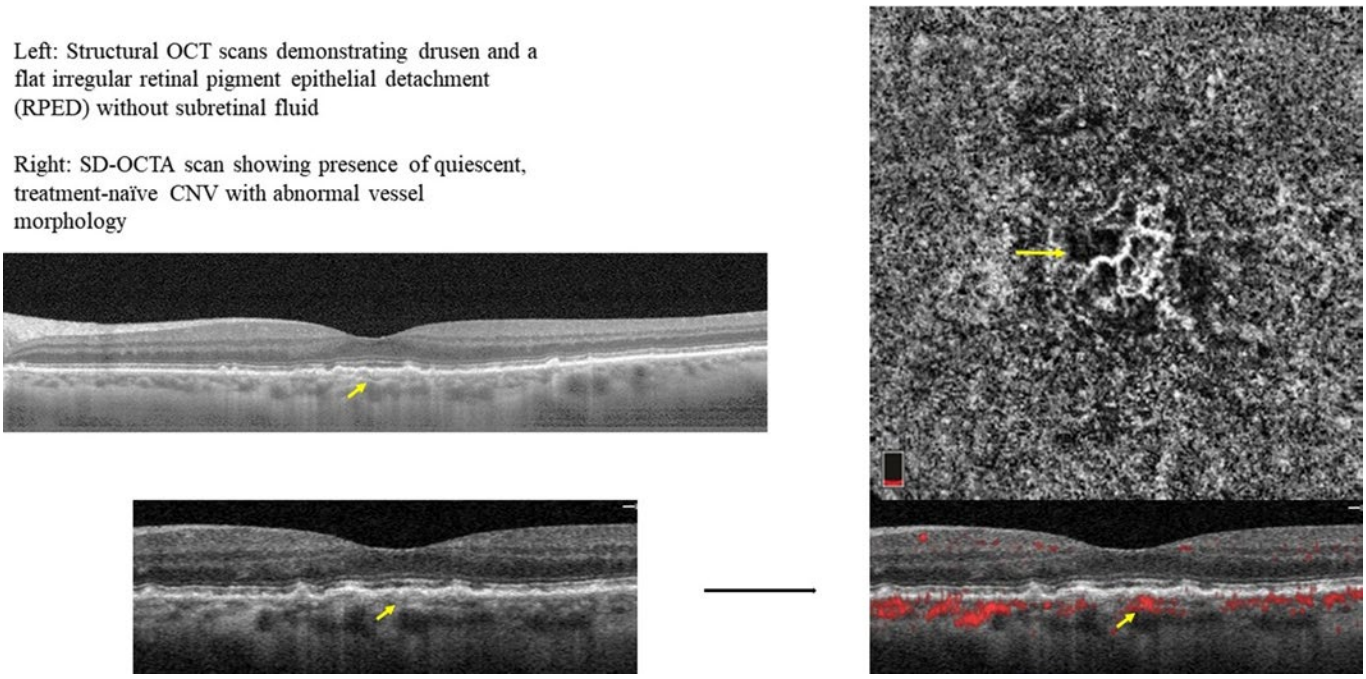

Figure 2. Visualization of treatment naïve, quiescent, nonexudative CNV of Dry AMD.

Diabetic Retinopathy—Diagnosis of Neovascularization

In addition to CNV, OCT-A is useful in diagnosing preretinal neovascularization of diabetic retinopathy (DR) as well.[8] Such detection may help differentiate between nonproliferative DR (NPDR) and proliferative DR (PDR). The flow overlay on structural B-scans may further assist in this differentiation by allowing distinction between intraretinal microvascular abnormalities (IRMA) and neovascularization (Arya, et al, unpublished data).

Intraretinal microvacular abnormality (IRMA) Lesion: OCTA showing intraretinal flow and no dye leakage on corresponding FA

Neovascular Lesion (PDR): OCTA showing supraretinal flow with confirming dye leakage on corresponding FA

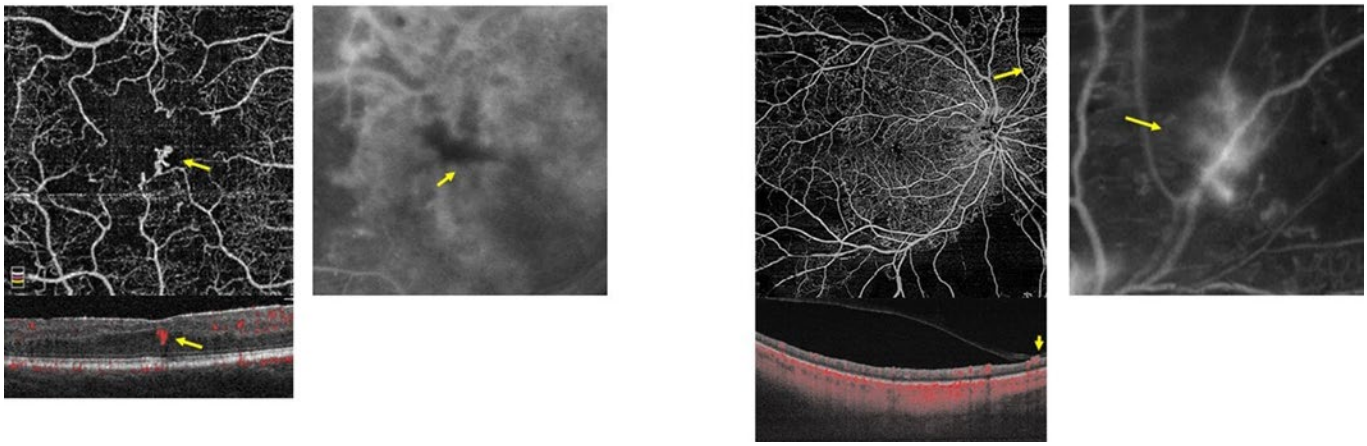

Figure 3. Visualization of IRMA and neovascular lesions on OCT-A.

Diabetic Retinopathy—Earlier Detection of Diabetic Retinopathy

OCT-A is comparable to FA in the evaluation of microvascular changes associated with DR.[9] However, it has also been able to detect retinal microvascular changes in diabetic patients without DR clinically or on FA.[10] Thus, OCT-A holds utility in diagnosing early DR that may not yet be detectable on clinical exam.

Retinal Vein Occlusions—Noninvasive Diagnosis

OCT-A is comparable to FA for diagnosing retinal vein occlusions.[11] It provides quick, noninvasive visualization of foveal avascular zone (FAZ) changes and areas of nonperfusion.[12]

Macular Telangiectasia—Noninvasive Diagnosis

OCTA's visualization of the macular changes associated with macular telangiectasia (MacTel) has been comparable to that of FA, fundus autofluorescence (FAF), and OCT.[13] Thus, it appears to be a useful imaging modality for the diagnosis of MacTel and in differentiating it from other retinal vascular pathologies, such as AMD.[14]

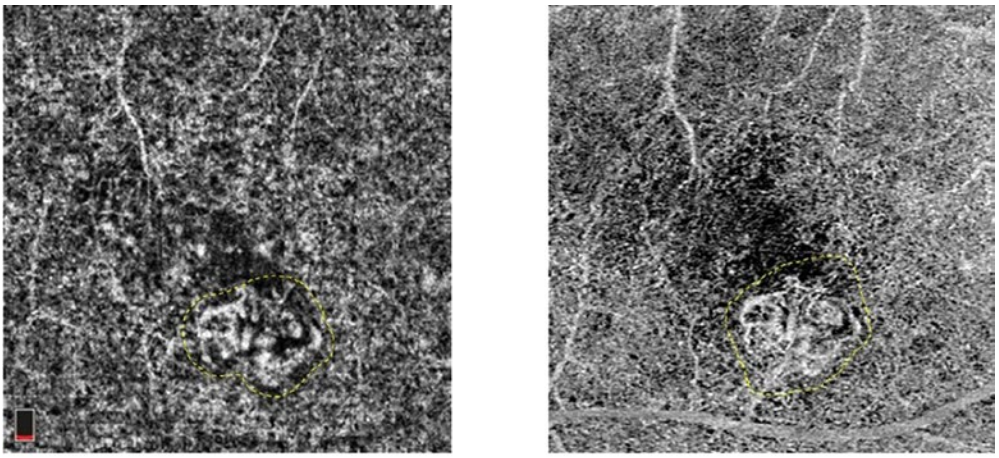

Figure 4. Comparison of CNV on spectral domain and swept source OCT-A.

The Improving Clinical Utility of OCT-A

Regarding wet AMD, due to its longer wavelength and thus improved depth-penetration, swept source OCT-A has demonstrated superiority over spectral domain OCT-A in visualizing CNV.[15] Automated algorithms quantifying CNV parameters have also been developed.[16]

The later stages of dry AMD, characterized by geographic atrophy (GA), involve changes in the photoreceptors, retinal pigment epithelium and Bruch membrane, and choriocapillaris. OCT-A, particularly swept source OCT-A, has allowed for visualization of the choriocapillaris, with studies demonstrating choriocapillaris loss under GA lesions and bordering flow impairment.[17] These findings suggest that choriocapillaris changes may precede outer retinal changes in GA, and OCT-A may have clinical utility in assessing the development and progression of dry AMD.

To further improve the utility of OCT-A in DR, the advent of "wide-field" OCT-A, with swept source OCT-A, may allow OCT-A to become a useful screening tool for DR by depicting peripheral microvascular abnormalities and nonperfusion. Because OCT-A provides a detailed view of the retinal capillaries, it is an ideal imaging modality for the screening and evaluation of DR. The foveal avascular zone (FAZ) is better delineated with OCT-A and has been shown to significantly increase from diabetic eyes without DR to eyes with each progressive stage of DR, from mild NPDR to PDR.[18] OCT-A measures of capillary nonperfusion, such as vessel density, have also been applied to DR. Compared to control eyes, vessel density has been shown to decrease in eyes with DR and progressively decrease with increasing DR severity.[19] Currently, OCT-A quantitative metrics differ in several factors, ranging from segmentation boundaries to calculation methodologies. With standardization of these metrics and the development of thresholds, quantitative OCT-A may be useful in screening for DR and assessing severity level.

Summary

OCT-A is a new, rapid, noninvasive imaging modality for visualizing the retinal and choroidal vasculature. It has demonstrated utility in a number of retinal pathologies, including AMD, DR, vein occlusions, and MacTel. Currently, there is great interest in the quantification of OCT-A to further expand its clinical utility.

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Are OCT Angiographic Images the Same Among Different Devices?

Giovanni Staurenghi MD

There are many OCT angiography (OCT-A) instruments on the market, and many others will be available in the near future. The hardware and software of these instruments are changing rapidly, and so all the data regarding software may be changed by the time of this presentation.

If we think about 2 possible different fluorescein angiography and indocyanine green angiography, the flash and the scanning laser based for OCT-A, we have a series of different approaches based on different algorithms. Here is a series of different approaches coming from the combination of at least 5 OCT-A methods:

1. Speckle variance (SV OCT-A)
2. Amplitude decorrelation (AD OCT-A)
3. Phase variance (PV OCT-A)
4. Combination of AD and PV
5. Probabilistic approach
6. And 2 averaging methods:
   a. Split spectrum
   b. Volume averaging

Shown below are some of the available imaging technologies used to create an OCT-A image:

- Phase Variance (CalTech University)
- OMAG: Optical microangiography (University of Washington: Zeiss - Angioplex and Kowa - OCT Bi-μ)
- CO-DAA: Complex OCT-signal differential analysis angiography (Nidek)
- SS-ADA: Split-spectrum amplitude-decorrelation angiography (Optovue - Angiovue)
- FS-ADA: Full-spectrum amplitude-decorrelation angiography (Canon-HS100)
- FSPA: Full-spectrum probabilistic approach (Spectralis, Heidelberg Engineering)
- OCT-ARA: Full-spectrum ratio-based amplitude ratio analysis (Topcon)
- PRD-OCT: Phase-resolved Doppler OCT (Amsterdam University)
- UHS-OCT-A: Ultrahigh speed swept source OCT angiography with VISTA (variable interscan time analysis) (MIT - Fujimoto)

The difference can be clinically visualized. Here is a series of possible differences:

- Different vessel sizes due to the different B-scan densities. Between B-scans each software fills the gap, and consequently the size of vessels and the space between vessels can vary. (See Table 1.)
- The detection of slow-filling vessels can be a challenge, and it can be detected or not. This can happen for microaneurysms, macroaneurysms, vessels in diabetic retinopathy and retinal vascular occlusions, and the bulge of polypoidal choroidal vasculopathy.
- Location of the segmentation to detect the different retinal vessels layers: This can be based on the structural OCT or on the highest signal location.

Table 1.

Company	Instrument	Source	Software	3x3 mm	Space between B-scans (μm)
Optovue	Avanti	SD-OCT	SS-ADA	304x304	9.9
Heidelberg Engineering	OCT2	SD-OCT	FSPA	512x512	5.7
Nidek	RS- 3000 Advance	SD-OCT	CO-DAA	256x256	11.7
Zeiss	Cirrus 5000	SD-OCT	OMAG	245x245	12.2
Canon	HS-100	SD-OCT	FS-ADA	232x232	12.9
Topcon	Triton	SS-OCT	OCT-ARA	320X320	9.4
Zeiss	Plex Elite	SS-OCT	OMAG	300X300	10.0

Abbreviations: SD-OCT, spectral domain OCT; SS-ADA, split-spectrum amplitude-decorrelation angiography; FSPA, full-spectrum probabilistic approach; CO-DAA, complex OCT-signal differential analysis angiography; OMAG, optical microangiography; FS-ADA, full-spectrum amplitude-decorrelation angiography; SS-OCT, swept source OCT; OCT-ARA, full-spectrum ratio-based amplitude ratio analysis.

Table 2.

Company	Instrument	Software Version	A-scan / B-scan	Vascular Plexus	Slab Boundary	Anatomic Basis	Offset
Optovue	Avanti	2016.1.0.2	304 / 304	Superficial	Top	ILM	3
					Bottom	IPL	15
				Deep	Top	IPL	15
					Bottom	IPL	71
Heidelberg Engineering	OCT2	SP 6.7a	512 / 512	Superficial	Top	ILM	0
					Bottom	IPL	0
				Deep	Top	IPL	0
					Bottom	OPL	0
Nidek	RS- 3000 Advance	AngioScan2	256 / 256	Superficial	Top	ILM	0
					Bottom	IPL	8
				Deep	Top	IPL	13
					Bottom	IPL	88
Carl Zeiss Meditec	Cirrus 5000	9.5.0.8712	245 / 245	Superficial	Top	ILM	0
					Bottom	IPL	0
				Deep	Top	IPL	0
					Bottom	OPL	0
Canon	HS-100	4.2	232 / 232	Superficial	Top	ILM	0
					Bottom	IPL	50
				Deep	Top	IPL	0
					Bottom	OPL	0
Optopol	Devo RX	7.0.0	512 / 300	Superficial	Top	ILM	5
					Bottom	IPL	0
				Deep	Top	IPL	15
					Bottom	IPL	70
Topcon Triton	1.17	1050 nm	512 / 512 320/320	Superficial	Top	ILM	3
					Bottom	IPL	16
				Deep	Top	IPL	16
					Bottom	IPL	70
Carl Zeiss Meditec	Plex Elite	1.5.0.15909	300 / 300	Superficial	Top	ILM	0
					Bottom	IPL	0
				Deep	Top	IPL	0
					Bottom	OPL	0

Abbreviations: ILM, internal limiting membrane; IPL, inner plexiform layer; OPL, outer plexiform layer.

Sickle Cell Retinopathy: New Findings From OCT/OCT Angiography

Jennifer I Lim MD

I. Spectral Domain OCT Findings in Sickle Cell Retinopathy

A. OCT subfield retinal thickness

1. Thinning in sickle cell (SC) vs. control eyes

a. Study of 513 SC eyes (260 patients) and 75 control eyes (39 patients) (Lim JI and Cao D)

i. OCT subfields showed significantly lower retinal thickness measurements for the central subfield ($P = .002$) and the nasal inner ($P = .009$), superior inner ($P = .021$), temporal inner ($P < .001$), inferior inner ($P = .017$), and temporal outer ETDRS subfields ($P = .012$).

ii. Thinning is most severe in the HgbSS subtype.

iii. Thinning is associated with Goldberg SC classification stage.

(a) various patterns of thinning despite the same SC stage

(b) various degrees of subfield thinning despite the same SC stage

iv. Thinning of OCT subfields correlates with age and with systemic diseases.

b. Study of 208 SC eyes (107 patients) and control eyes (Matthew R, Bafiq R, Pearce E, Richardson M, Drasar E, Thein SL, Siviprasad S)

i. 44% of the eyes of patients with SC disease (SCD) show discrete areas of retinal thinning in the temporal macular area.

ii. Proliferative SC retinopathy is more prevalent in eyes with thinning than in SCD eyes with normal macular morphology (67% vs. 48%; $P = .0017$).

iii. The temporal total and inner retinal thickness, macular volume, and choroidal thickness are significantly lower in patients with SCD compared with age-, gender-, and ethnicity-matched controls.

2. Areas of thinning have decreased function on MP-1 testing (Chow CC, Genead MA, Anastasakis A, Chau FY, Fishman GA, Lim JI).

B. OCT retinal nerve fiber layer (RNFL) thickness (Chow C, Shah RJ, Lim JI, Chau FY, Hallak JA, Vajaranant TS)

1. Study of 151 eyes in 88 SC patients and 55 eyes of 30 controls

2. Eyes with OCT macular thinning have thinner mean peripapillary RNFL thicknesses in the nasal ($P = .01$) and superotemporal sectors ($P = .01$)

3. Degree of thinning correlates with severity of temporal macular thinning.

C. Longitudinal study of RNFL (Thavikulwat A, Cao D, Vajaranant TS, Lim JI)

1. Peripapillary RNFL thickness decreases at a rate of 0.98 (95% CI, 0.77-1.19) µm/year.

2. Inferonasal and inferotemporal subfields have greatest rates of thinning at 1.92 (95% CI, 1.32-2.52) and 1.94 (95% CI, 1.43-2.45) µm/year, respectively.

3. Prior stroke is associated with an increased rate of global RNFL thinning ($P < .001$).

4. Hypertension is associated with a decreased rate of thinning ($P < .01$).

II. OCT Angiography Findings

A. Qualitative study of 82 eyes (46 patients) with SCD (Han IC, Tadarati M, Pacheco KD, Scott AW)

1. Discrete areas of flow loss are seen in 37.8%.

2. Flow loss is more extensive in SC subtype or proliferative stages.

B. Quantitative comparison of OCT angiography (OCT-A) of 36 SC with 26 control eyes (Alam M, Thapa D, Lim JI, Cao D, and Yao X)

1. Blood vessel tortuosity is seen more often in SC eyes: 48% SC vs. 31.5% control eyes ($P < .001$, Cohen's d = 3.69).

2. Vessel diameter is 29.4% increased in SC vs. control eyes ($P < .01$, Cohen's d = 3.18).

3. Vessel perimeter index of superficial layer is decreased in SC vs. control eyes; 8.31% vs. 10.8% ($P < .05$, Cohen's d = 2.41).

4. Area of foveal avascular zone (FAZ) is increased in superficial (52%) and deep (53%) layers for SC vs. control eyes ($P < .001$, Cohen's d = 4.15).

5. Contour irregularity of FAZ
    a. Irregularity and spiculation increased by 36%
    b. Deviation from an ideal circular contour is greater in SC.
        i. SC: 46%-47% deviation
        ii. Controls: 10%
        iii. $P < .001$, Cohen's d = 4.52
6. Parafoveal avascular density is significantly different between SC and control eyes.

C. Quantitative comparison between SC retinopathy stages (Alam M, Thapa D, Lim JI, Cao D, and Yao X)
    1. Vascular tortuosity, FAZ area, FAZ contour irregularity, and avascular blood vessel density of SC retinopathy stage 2 and stage 3 eyes significantly differ from control eyes.
    2. Differences are greater between control and stage 3 PSR eyes than between control and PSR 2 eyes.

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OCT Angiography Smash Hits

Nadia K Waheed MD

Introduction

OCT angiography (OCT-A) is a relatively new imaging modality that is being integrated into clinical practice. It has utility across a range of choroidal and retinal vascular diseases. This presentation will focus on clinical applications of OCT-A. I will look at a series of cases of retinal disease where OCT-A assisted in either the diagnosis or the management.

Choroidal Neovascularization

OCT-A is useful in the diagnosis and monitoring of patients with choroidal neovascularization secondary to AMD and other etiologies, such as central serous choroidopathy, presumed ocular histoplasmosis, and pathologic myopia.

Retinal Vascular Disease

OCT-A can be used to monitor the retinal vascular changes associated with retinal vascular diseases such as diabetic retinopathy. It is also useful in the identification and follow-up of retinal neovascularization.

Cases presented will highlight these aspects of the utility of OCT-A.

Imaging the Neurovascular Unit

Richard F Spaide MD

The Neurovascular Unit

The retina is a complex structure with many interconnected parts. It has neuronal cells to help detect and process visual information, glial cells to modulate the environment for the neuronal cells, and blood vessels to supply to provide food, oxygen, and access to the immune system. The combination of all of these is called the neurovascular unit. Diseases of the retina affect all of these components to one degree or another, even though we commonly only evaluate one of these systems for any particular disease. To understand disease, and potentially to be able to recognize new diseases as well as to predict future outcomes, knowing how the neurovascular unit is affected will provide more information than looking at one structure in isolation. We could try to image the system, or parts of the system, with multiple imaging methods to gain a more complete idea of the retina.

Over the last few years multimodal imaging has added to our understanding of the retina. In multimodal imaging several types of imaging are done, typically of a structure or lesion, and we gain information from each imaging modality and then assemble the parts of information into a mental picture. This is a powerful technique, and it can encourage thinking about elements of the retina in isolation. The retina is a system of interlocked components, and the next step in retinal imaging will include recognizing how these components work together.

Weather Analogy

If we want to predict weather, we don't just look at a portion of the sky with infrared, blue, and green light and come up with a forecast. We don't use multimodal imaging of the sky to predict if there will be rain in two days. Instead, meteorologists evaluate thousands of variables such as temperature readings from many points on the ground and in the air, weather fronts and their movements, and high and low atmospheric pressure measurements. The data accumulated are used to understand the weather system and its likely future course for any given region. We can take a similar systems approach to understanding the retina by using various imaging modalities.

Systems Imaging

We can image the full thickness of the retina and segment various layers. The ganglion cell layer contains the cell bodies of the ganglion cells, but it also contains Müller cells, astrocytes, and blood vessels. Diseases such as glaucoma affect ganglion cells, but what about blood vessels? Are they secondarily affected if there are fewer ganglion cells to supply? Retinal vascular problems like diabetes affect the blood vessels, but if there is a microcirculatory problem, one would expect the supplied cells, such as the ganglion cells (for the superficial vascular network), to be affected as well. The nerve fiber layer is composed of nerve fibers, glial cells, and blood vessels. In glaucoma the nerve fiber layer thins. What about the blood vessel density? If diabetes causes circulatory problems in the superficial vascular layer and the ganglion cell layer changes, does the nerve fiber layer change as well? The nerve fiber layer is supplied by the radial peripapillary capillary network. How is this affected by concomitant nerve fiber layer changes? As it turns out, diabetes does affect the ganglion cell layer thickness in a profound way, but it has much less of an effect on the nerve fiber cell layer. Using discriminant analysis with ganglion cell layer thickness, nerve fiber layer thicknesses, and retinal vascular and radial peripapillary OCT angiography–derived indices, efficient classification of disease is possible that is better than using fewer test modalities.

Opportunity for Machine Learning and Big Data

Weather forecasting was one of the first widespread uses of big data to handle the thousands of pieces of information required to make an accurate forecast. With the ease and speed of modern fundus imaging, we can obtain big data from the eye. We don't know how all of it fits together at present because this kind of data hasn't been adequately evaluated, particularly over long-term follow-up. The era of evaluating imaging studies using pattern recognition of gross manifestations is likely to be superseded by more complex computer-driven evaluations of patterns and changes not recognizable by humans. In addition, the large amount of data that potentially could be produced is difficult to integrate, even if a human could recognize patterns. Machine learning could analyze the available information, nearly instantaneously, and potentially provide diagnostic information and expected outcomes. This is a big change from the present, but it will allow for more accurate diagnostic and prognostic capabilities than what we do today.

New Modes of Autofluorescence Imaging

Frank G Holz MD

I. Fundus Autofluorescence

A. Imaging techniques based on retinal autofluorescence have found broad applications in ophthalmology because they are extremely sensitive and noninvasive.

B. Fundus autofluorescence (FAF) imaging allows for in vivo mapping of naturally or pathologically occurring fluorophores of the ocular fundus, which provides additional insights into metabolic processes of the retina.

C. Applications include refined phenotyping and differential diagnosis of retinal diseases, identification of early disease stages to allow for earlier intervention and better outcomes, monitoring disease progression in the context of natural history and interventional studies, identification of prognostic biomarkers, novel clinical endpoints closely linked to visual function, and luteal pigment measurements.

II. Techniques of Fundus Autofluorescence Imaging

A. Imaging devices include (confocal) scanning laser ophthalmoscopy and fundus camera–based systems.

B. Blue autofluorescence (BAF)

1. Emission light wavelength typically 488 nm
2. Currently most commonly used and extensively studied

C. Green autofluorescence (GAF) imaging

1. Longer emission wavelength (eg, at 514 nm)
2. Less luteal pigment absorption and thus better visualization of foveal alterations
3. Less absorption by the crystalline lens
4. Structural information comparable to BAF

D. Near-infrared autofluorescence (NAF) imaging

1. Obtainable in vivo by using the indocyanine green angiography mode without dye injection
2. Due to the excitation and emission in the red end of the spectrum, the topographic distribution of fluorophores other than lipofuscin can be studied.
3. The signal is largely melanin derived and spatially related to the retinal pigment epithelium monolayer and choroidal melanin.

E. Wide-field imaging

1. FAF recordings beyond the vascular arcades are helpful for assessment of the peripheral alterations associated with retinal diseases.
2. The standard image field of the typical confocal scanning laser ophthalmoscope (cSLO) encompasses a retinal field of 30° × 30°. Additional lenses allow for imaging of a 55° field or, using the composite mode, imaging over larger retinal areas.
3. Wide-field scanning laser ophthalmoscopes are available covering a field > 55° (Optos PLC; Scotland, UK)
4. Montage images can be generated when smaller frames are recorded using image analysis software.

F. Macular pigment mapping

1. Macular pigment consists of lutein and zeaxanthin that accumulates along the axons of the cone photoreceptors in the central retina.
2. Functions for macular pigment include filtration of blue light which may reduce photo damage and glare, minimization of the effects of chromatic aberration on visual acuity, improvement in fine-detail discrimination, and enhancement of contrast sensitivity.
3. Peak absorption of luteal pigment is at 460 nm. These absorption properties can be recorded in vivo by blue-light autofluorescence imaging.
4. Two-wavelength (blue and green) FAF method is optimal for quantification and topographic information of luteal pigment distribution.
5. Compared to other methods, including heterochromatic flicker photometry, the advantage of FAF imaging is its objective acquisition technique, which is not dependent on psychophysical cooperation by the patient.

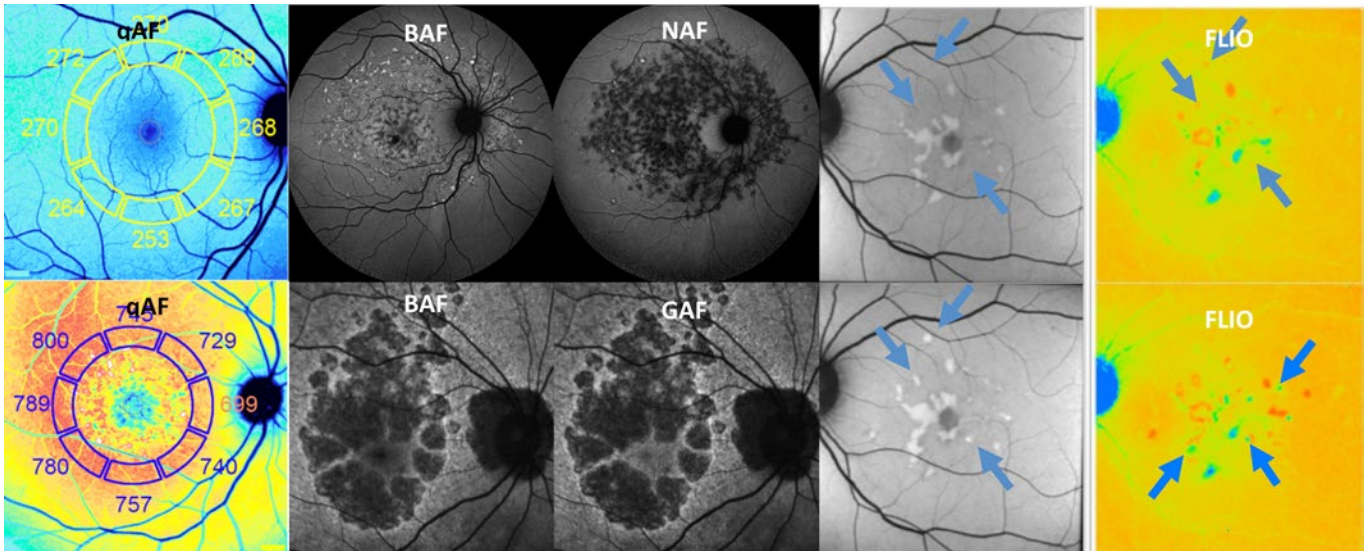

Figure 1. Top left: Quantitative autofluorescence (qAF) in a normal individual and (lower left) in a patient with Stargardt disease and markedly increased levels of fluorescence (excitation 488 nm).[7,8] Top middle pair: blue autofluorescence (BAF) and near-infrared autofluorescence (NAF) in a patient with Stargardt disease showing more widespread disease at the level of the RPE layer. Lower middle pair: blue autofluorescence (BAF) and green autofluorescence (GAF) (excitation 514 nm) in presence of geographic atrophy due to AMD; note less absorption by macular pigment in the GAF image with similar structural information outside.[2] Top and lower right pair: fluorescence lifetime imaging ophthalmoscopy (FLIO) in a patient with Stargardt disease: short (red) flecks (short FLT) are partly not yet visible in the FAF intensity image. Three years later, red flecks become visible in FAF intensity image and over time change to blue (long FLT) flecks.[10]

III. Novel Modes of Autofluorescence Imaging

A. Fluorescence lifetime imaging ophthalmoscopy (FLIO)

1. Noninvasive technique to measure and quantify lifetimes of endogenous retinal autofluorescence
2. When endogenous fluorophores are excited by photons derived from a monochromatic light source, they gain a higher level of energy before returning to their ground state by emitting photons of longer wavelengths than the exciting light.
3. The average time between excitation and reaching the ground state again can be quantified as the "fluorescence lifetime."
4. Can be applied to detect weakly fluorescing fluorophores if they differ in their lifetime
5. Whereas conventional FAF provides spacially resolved information on fluorescence intensities, FLIO additionally measures fluorescence lifetimes or decay times and thereby includes time as a third dimension (space and time resolved).
6. According to their wavelength, photons are separately detected in 2 channels: a short spectral channel (wavelength 498-560 nm; SSC) and a long spectral channel (560-720 nm; LSC).
7. FLIO is based on a Heidelberg Retina Angiograph cSLO (HRA2, Heidelberg Engineering; Germany) (Dysli et al, 2014b).
8. Recent reports have contributed to the understanding of the pathophysiology of various macular and retinal diseases including AMD, Stargardt disease, diabetic retinopathy, and macular telangiectasia type 2.

B. Quantitative autofluorescence (qAF) imaging

1. A cSLO device (Spectralis HRA, Heidelberg Engineering) is equipped with an internal fluorescent reference to account for fluctuations in laser power and differences in detector sensitivity.
2. The visual pigment is bleached for at least 20 seconds prior to recording.
3. qAF mode: 486-nm excitation and 500-680 nm detection
4. A series of successive images is recorded (30° field of view and 768×768 pixels); a minimum of 9 remaining images are typically required for analysis.
5. The mean gray values of the reference and a circular region with eight subsegments and an eccentricity of approximately 7° to 9° centered on the fovea are typically measured.
6. New insights into the pathogenesis of various retinal diseases and helpful for differential diagnosis
7. Potential new outcome parameter in interventional clinical trials
8. Challenge: corrections for lens opacifications

C. "Color" autofluorescence FAF imaging

1. New confocal blue-light FAF device (EIDON, CenterVue; Padua, Italy) using a 450-nm wavelength and light-emitting diode (LED) light source and emission detection between 500 and 750 nm
2. A different range of fluorophores are excited, at 450 nm compared with 488 nm.
3. There are challenges in isolating the signal from minor fluorophores as the magnitude of the emission signal may be relatively weak.
4. The confocal LED blue-light FAF system: potential advantage in that the full-emission spectrum is detected on a color sensor
5. The emission spectrum can be divided into long-wave and short-wave emission components ("red" [560-700 nm] and "green" [510-560 nm]).
6. Advantage for isolating minor fluorophores whose emission spectrum might otherwise be overwhelmed by the strong emission of lipofuscin in the longer wavelength end of the emission spectrum

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Multimodal Pediatric Retinal Imaging for Vitreoretinal Surgical Planning

Cynthia A Toth MD

Pediatric vitreoretinal surgery is performed for a wide range of vitreoretinal conditions. Retinal imaging in these patients depends on the differential diagnosis and the proposed interventions. Pediatric retinal surgical planning may benefit from perioperative imaging, which can be important to assess, document, compare over time, and communicate the disease processes and severity / stage of disease.

Pediatric care extends from premature infants to young adults, and imaging techniques vary by the patient's ability to cooperate and fixate for imaging. These imaging techniques (#1-4 below) are used in clinic or during examination under anesthesia. Imaging younger patients in clinic may require avoiding long wait times and using illuminated toys or cell phones and an additional assistant during imaging.

1. Color fundus photographs
   - In clinic, it is often easier to perform a detailed examination for nuanced details in the photograph in contrast to the ophthalmoscopic retinal examination, which may be more limited.
   - Although macular / posterior pole imaging is of great use, wide-field imaging is important, especially in diseases with peripheral pathology such as retinal detachment, Coats disease, familial exudative vitreoretinopathy (FEVR), and ROP.
2. Fluorescein angiographic imaging
   - This provides critical information about vascular perfusion, avascular retina, vascular abnormalities, neovascularization, leakage, retinal pigment epithelial abnormalities, and choroidal abnormalities.
   - Oral fluorescein angiography may be an alternative to intravenous imaging in clinic.
   - Wide-field fluorescein angiographic imaging is especially critical in differentiating multiple pediatric conditions that may not be identified from macular imaging alone, including Coats, FEVR, and ROP. In cases of epiretinal membrane, angiography may be very useful in diagnosing combined hamartoma of the retina and retinal pigment epithelium.
   - This imaging may still be useful in eyes where cataract interferes in part with conventional photographs.
   - Allergic response can occur in response to fluorescein dye, with a risk of approximately 1/200,000.
3. OCT
   - As with adult retinal diseases, OCT provides important information about the vitreoretinal interface even in cases without apparent epiretinal tissue.
   - In reviewing OCT images, it is also important to review for abnormal pre- and subretinal tissue, and/or preoperative inner, outer, and subretinal changes. These may not be apparent from photographs and, as with adult surgery, may guide surgical planning.
   - OCT angiography has been performed with commercially available and with investigational devices in research imaging in infants and children and may provide additional information about retinal vascular and choroidal flow.
4. Ocular ultrasound
   - Especially when the view to the retina is limited by corneal opacity, cataract, or vitreous hemorrhage / opacity, B-scan ultrasound provides valuable information about the globe, choroid and vitreous, and retinal configuration. In eyes with suspicion for retinoblastoma, this is important in examining for retinal configuration and for calcifications.
   - Measurement of axial length (in both eyes for comparison) from A-scan ultrasound or other measures is important in identification of persistent fetal vasculature, axial myopia, or glaucoma.
5. MRI
   - Useful especially in evaluating in cases suspicious for retinoblastoma, in which case high-resolution contrast-enhanced MRI is generally useful to evaluate extent of disease. Note that radiation exposure of CAT scan is avoided in these evaluations.

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Swept-Source OCT and OCT Angiography for Pathologic Myopia

Kyoko Ohno-Matsui MD

Pathologic myopia (PM) is a major cause of visual impairments worldwide and especially in east Asia. The visual impairments are caused mainly by 3 complications occurring in the posterior fundus: (1) optic nerve damage, (2) myopic choroidal neovascularization (myopic CNV), and (3) myopic macular retinoschisis (MRS). The main cause of these complications is the eye deformity induced by posterior staphylomas.

The advance of new imaging technology has greatly enhanced the knowledge of the different pathological alterations caused by PM. This is especially true for the swept source ultrawide-field OCT (WF-OCT) and swept source OCT angiography (OCT-A) instruments.

The swept source WF-OCT prototype is a powerful device that can be used to examine tissues at different depths, from the vitreous to the deeper choroid and sclera, in one very wide angle image. This allows the clinician to observe the spatial relationship between the scleral contour and the myopic vitreoretinal complications.

The OCT-A device is especially useful for diagnosing and determining the activity of myopic CNVs.[1] Swept source OCT-A examinations of highly myopic eyes have allowed investigators to detect the feeding vessels situated deep in the sclera.

Ultrawide-field OCT (WF-OCT) to Examine Posterior Staphylomas

A posterior staphyloma is a hallmark alteration of eyes with PM, and it has been defined by Spaide[2] as an outpouching of the ocular wall with a radius of curvature shorter than that of the surrounding ocular wall. Highly myopic eyes with posterior staphylomas have significantly poorer visual and anatomical prognosis than highly myopic eyes without staphylomas. The most common type of staphyloma is the wide macular staphyloma,[3] which does not fit within the scan length of a conventional OCT device. A prototype WF-OCT device (Canon Co.; Japan) has been developed that can analyze a region of interest of up to 23 mm × 20 mm and a depth of 5 mm. With the WF-OCT device, it is possible to obtain images of posterior staphylomas in highly myopic eyes in their full 3-dimensional extent.[4] The data obtained by WF-OCT should be important for future analyses and therapies for staphylomas before vision-threatening complications develop.

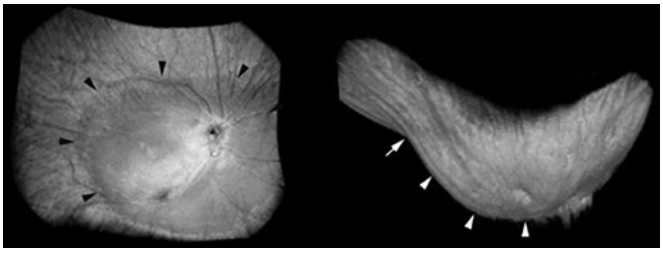

Figure 1.

Ultrawide-field OCT to Examine Myopic Macular Retinoschises and Their Spatial Relationship to Staphylomas

A macular retinoschisis (MRS) is present in 9% to 34% of highly myopic eyes. Previous studies have shown that a combination of various mechanisms could lead to the development of macular retinoschisis. WF-OCT clearly showed that the sites of the MRS and staphylomas were spatially related.[5] Observations of the vitreous and the deeper tissues up to the sclera in the very wide angle images showed a posteriorly directed force in association with staphylomas, and an inwardly directed force due to epiretinal membranes or vitreoretinal attachments. These opposing forces may be the causative factors for MRS formation. The data obtained by WF-OCT could be useful for making surgical strategies for MRS.

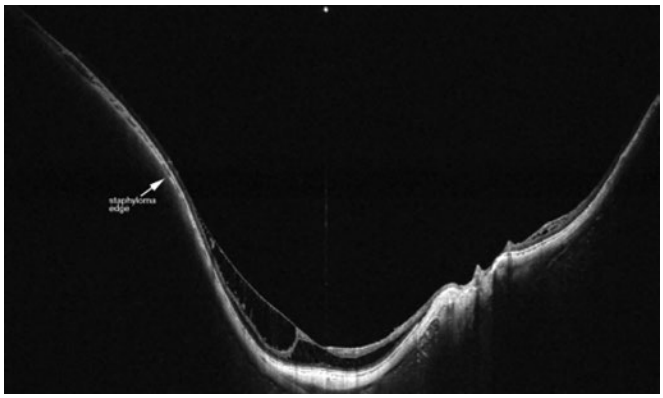

Figure 2.

Ultrawide-field OCT to Examine Vitreal Changes Occurring in Pathologic Myopia From Childhood to Adulthood

The swept source WF-OCT images have shown that the abnormal changes in the vitreous of highly myopic eyes are present even in early childhood, and they also showed how the vitreal changes progressed with increasing age in parallel with changes of the scleral contour.

Swept Source OCT and OCT-A for Myopic CNVs

The OCT-A can obtain en face images of the vascular network that is detectable by the blood flow in eyes with an active myopic CNV.[1] Except for very small CNVs, blood flow is maintained even when a myopic CNV becomes a scar and even in the atrophic phase (ie, CNV-related macular atrophy).

Myopic CNVs have been considered to originate mainly from the choroidal capillaries even though the choroid is extremely thin in eyes with PM.[6] However, Louzda et al[7] recently reported a case where myopia was associated with an intrascleral blood vessel in the en face OCT-A images. Our

ongoing studies have also shown that some of the myopic CNVs had feeder vessels from the sclera which communicated with the CNV directly or through a thin choroid sandwiched between them. These data indicate that a myopic CNV is not "choroidal," at least in some cases.

Conclusions

Swept-source OCT and OCT-A are powerful tools to investigate detailed morphology of myopic fundus lesions and also to clarify how staphylomas cause such vision-threatening complications.

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Hyper-reflective Foci: A Relevant Biomarker for Macular Disease Activity

Ursula Schmidt-Erfurth MD, Bianca S Gerendas MD, Amir Sadeghipour PhD, Sebastian M Waldstein MD PhD, Thomas Schlegl Dipl.-Ing, and Hrvoje Bogunović PhD

HRF in Retinal Imaging

Diagnostic imaging in macular disease using high-resolution 3-dimensional raster scanning by OCT offers identification and quantification of subclinical biomarkers such as drusen area and volume, neurosensory layer thickness, and hyper-reflective foci (HRF).

HRF appear as small, well-defined intraretinal lesions with equal or higher reflectivity than the retinal pigment epithelium (RPE) and are primarily defined as optical features independent of their pathophysiological origin. HRF have been shown as a biomarker associated with exudative macular diseases such as diabetic macular edema (DME), choroidal neovascularization (CNV), retinal vein occlusion (RVO)[1,2] and with degenerative macular / retinal disease such as AMD, including geographic atrophy (GA), Morbus Stargardt, and retinitis pigmentosa (RP). In exudative conditions, HRF was related to lipid exudates, while neurodegeneration migration of the RPE has been suggested as a pathophysiological correlate.[3,4] Location and quantity of HRF have been proposed as prognostic factors for disease activity and visual outcome.

Automated Segmentation of HRF Using Machine Learning

Automatic detection of disease-related entities in retinal imaging data is relevant for disease and treatment monitoring. It enables a quantitative assessment of large amounts of data and the corresponding study of disease characteristics. The presence of HRF is related to disease progression in various retinal diseases. Manual identification of HRF in spectral domain OCT (SD-OCT) scans is error-prone and tedious, with the dataset usually consisting of hundreds to thousands of B-scans. We developed a fully automated machine learning approach for segmenting HRF SD-OCT scans using a semantic segmentation methodology. We leverage deep learning–based semantic segmentation to obtain a mapping from intensity images to corresponding images of dense pixel-level class labels. The underlying feed-forward neural network comprises two main building blocks, which are jointly trained. First, an encoder transforms the input image into a low-dimensional abstract context representation. Secondly, a decoder maps the low-dimensional embedding (ie, the output of the encoder) to a full-input resolution image of corresponding class label predictions. The most basic processing units of encoder and decoder are convolutional layers. Typically, the encoder produces successively smaller resolution feature maps through the utilization of strided convolutions or convolution with stride 1 followed by a pooling layer. The decoder produces successively larger resolution images through the utilization of the unpooling operation, or implementing fractionally strided convolutions. The network is trained end-to-end; that is, parameter updates in every update iteration are based on tuples of intensity images and corresponding images of target labels.

Furthermore, we proceeded with a residual U-Net–based semantic segmentation: the U-Net architecture is based on a contracting path (encoder) and an expanding path (decoder). The main contribution of Ronneberger et al in the conception of the U-Net architecture is the concatenation of the feature maps of every layer of the encoder with the feature maps of the corresponding level of the decoder. In this way, higher-resolution context information can be propagated to the last decoder layers, which improves localization and allows precise segmentation. The main building blocks of ResNet are residual units. Residual units learn not only the mapping from inputs to outputs, but also residual functions between inputs and outputs of individual layers, thus allowing even very deep networks learning the identity mapping. Residual units implement shortcut connections, which perform the identity mapping by skipping one or more layers. The outputs of the shortcut connections are added to the outputs of the skipped layers. Since shortcut connections do not add further model parameters, or increase the computational complexity, end-to-end training of even very deep networks by stochastic gradient descent (SGD) is enabled.

Both architectures can be combined to build up a residual U-Net (ResUNet), a deep neural network for semantic segmentation with a U-Net architecture, with residual units as individual layers.

Evaluation on annotated OCT images of the retina demonstrated that a residual U-Net allows us to segment HRF with high accuracy. As our dataset comprised data from different retinal diseases, including AMD, diabetic macular edema, and retinal vein occlusion, the algorithm can safely be applied in all of them even though different pathophysiological origins are known.[5] Results demonstrated solid applicability of all examined HRT segmentation algorithms for both OCT devices, Cirrus and Spectralis.

The Role of HRF in AMD Conversion

HRF were segmented with a deep learning approach based on a convolutional neural network (CNN) in 495 fellow eyes presenting with intermediate AMD in a prospective study over 2 years. The CNN was trained on ≈550 manually annotated B-scans containing HRF, from 46 patients with CNV, diabetic macular edema, or retinal vein occlusion. The training set scans were acquired with the same OCT device model (Cirrus, Zeiss) and were disjoint from the set of scans used in our study. Representative HRF segmentations are shown in Figure 1.[5]

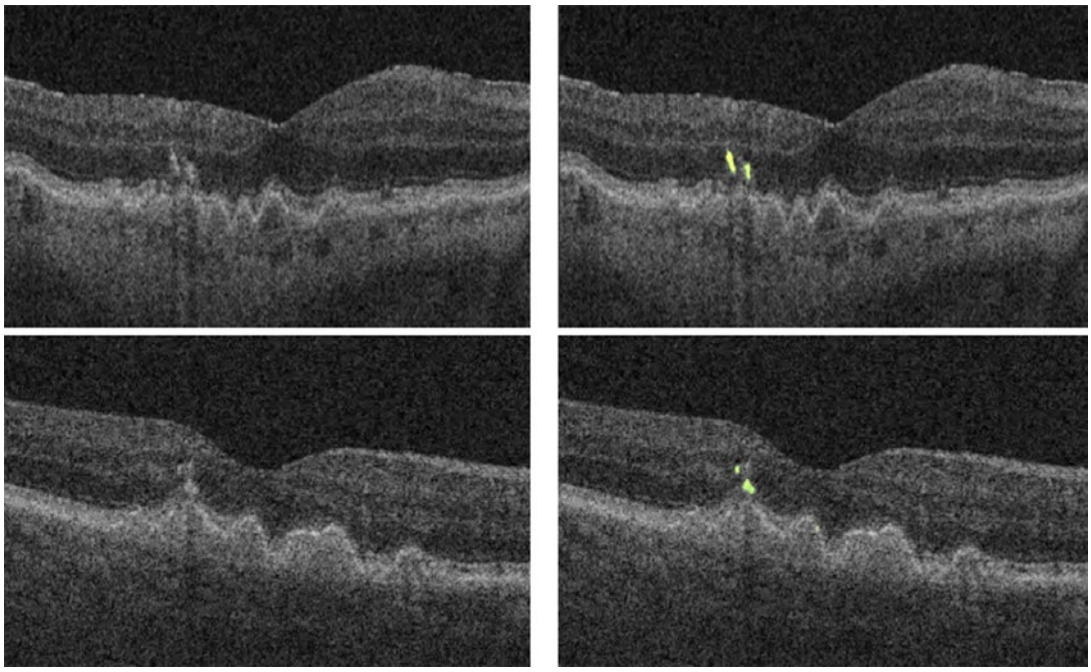

Figure 1. Example of automated hyper-reflective foci segmentation (overlayed in yellow) within neurosensory layers (Schlegl, et al, 2018).

HRF are also associated with GA development. Yet their appearance was rather diffuse throughout all layers of the retina and RPE. HRF were described as precursors of GA development by several authors, such as Christenbury et al in a study of 299 AMD eyes showing a high correlation of GA development at 2 years with the presence of baseline HRF, greater number of baseline HRF and greater axial HRF distribution.[6] High-speed ultrahigh-resolution OCT depicted HRF as intraretinal RPE migration.[7] A correlation of histology and SD-OCT features by Curcio et al confirmed the highly prognostic role of intraretinal RPE cells and suggested HRF monitoring for obtaining a timeline of incipient GA in clinical populations and for anatomic endpoints in clinical trials.[8] The project MACULA by Curcio et al offers a RPE grading system for histology and OCT in AMD explaining the role of RPE shedding and migration as a pathognomonic feature of AMD disease.[9] Advanced imaging analyses offer the same insight in vivo and over time in an individual patient.

HRF was also a leading prognostic marker of conversion toward CNV. For neovascular progression, HRF location was, however, associated with drusen, in contrast to the diffuse retinal distribution seen in GA development.[10]

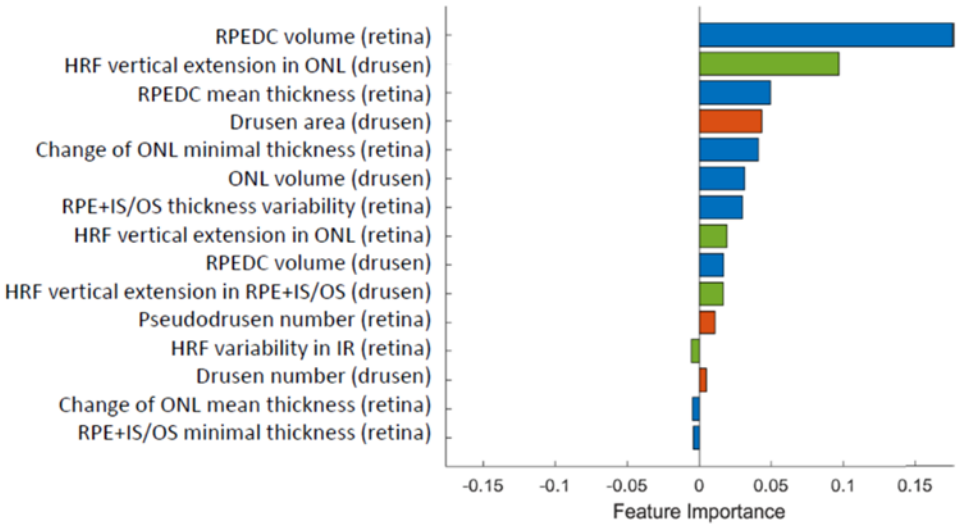

Figure 2. Predictive model of CNV conversion. Top 15 most important features with their regions of interest (drusen)-centric or (retina)-wide, expressed as a mean signed weight assigned to layer-related (blue), HRF-related (green) and drusen-related (red) features.

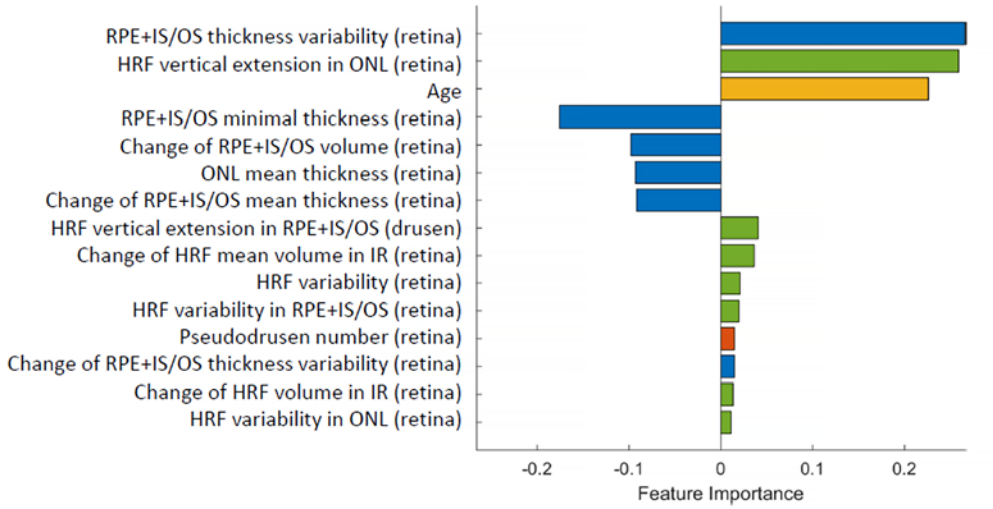

Figure 3. Predictive model of GA conversion. Top 15 most important features with their region of interest (drusen)-centric or (retina)-wide, expressed as a mean signed weight assigned to layer-related (blue), HRF-related (green), drusen-related (red), and non-imaging (yellow) features.

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Phase 3, Randomized, Double-Masked, Multicenter Trials of Brolucizumab vs. Aflibercept for Neovascular AMD: Ninety-Six-Week Results From the HAWK and HARRIER Studies

Pravin U Dugel MD, Glenn Jaffe MD, Ursula Schmidt-Erfurth MD, Yuichiro Ogura MD PhD, Adrian Koh MBBS FRCS MMed FRCOphth FAMS, Georges Weissgerber MD, Andreas Weichselberger PhD, Zuhal Butner OD MS MBA, and Frank G Holz MD

Intravitreal anti-VEGF therapy represents the first-line treatment for neovascular AMD (nAMD). While currently available anti-VEGF agents provide robust improvements in functional outcomes in patients with nAMD, the burden of frequent injections and monitoring visits often results in reduced patient adherence, leading to undertreatment and suboptimal visual outcomes.[1-3] New effective treatment modalities with prolonged duration of action are therefore needed to address these challenges for patients, caregivers, and treating clinicians.[1-3]

Brolucizumab, a novel anti-VEGF molecule (also known as RTH258), is a unique, small (26 kDa) single-chain (scFv) antibody fragment that has been designed with an innovative technology platform specifically for ophthalmic use.[4-6] The small molecular design of brolucizumab enables greater molar dosing, thus providing the potential for long-lasting effect and effective retinal tissue penetration relative to larger anti-VEGF agents.[7] At present, brolucizumab is the most clinically advanced scFv in development for therapeutic application.[6]

Here we present the results from 2 global, randomized, masked Phase 3 studies, HAWK and HARRIER, designed to compare the efficacy and safety of intravitreal injections of brolucizumab with that of aflibercept in patients with nAMD.[8,9] HAWK and HARRIER are the first Phase 3 studies to evaluate an exclusive q12w dosing regimen immediately after the loading phase.

HAWK and HARRIER were 96-week prospective, double-masked, multicenter studies in which patients were randomized 1:1:1 to brolucizumab 3 or 6 mg or aflibercept 2 mg (HAWK) or 1:1 with either brolucizumab 6 mg or aflibercept 2 mg (HARRIER). Following the 3-month loading phase, patients in the brolucizumab arms received q12w dosing with an option to adjust to q8w dosing based on masked disease activity assessments at predefined visits. Aflibercept was dosed at q8w intervals in both studies. Combined, these studies enrolled >1800 patients across 400 centers globally.

The primary objective of both HAWK and HARRIER was noninferiority (margin: –4.0 letters) of brolucizumab to aflibercept in BCVA change from baseline to Week 48. Secondary objectives included assessment of anatomical, visual, and safety outcomes.

In both studies, the primary endpoint was met; brolucizumab was noninferior to aflibercept for the mean change in BCVA at Week 48 (HAWK: $P = .0003$ [3 mg]; $P < .0001$ [6 mg]; HARRIER: $P < .0001$). Brolucizumab 6 mg patients also demonstrated reduced disease activity during the matched treatment phase (HAWK: $P = .0010$; HARRIER: $P = .0019$) and statistically superior reductions in central subfield thickness vs. aflibercept at Week 16 (HAWK: $P = .0016$; HARRIER: $P < .0001$) and Week 48 (HAWK: $P = .0023$; HARRIER: $P < .0001$). These visual and anatomical outcomes were achieved with a significant proportion of brolucizumab 6 mg patients, maintained exclusively on a q12w treatment interval through to Week 48. Overall ocular and non-ocular adverse event rates of brolucizumab were comparable to those of aflibercept at Week 48.

Brolucizumab has the potential to reduce the high treatment burden in patients with nAMD. The HAWK and HARRIER studies demonstrated significant visual gains and anatomical improvements with brolucizumab over the 48-week period. The 96-weeks results from the two studies will be presented.

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Late Breaking Developments, Part II

Use of Intravitreal Aflibercept Treat-and-extend Dosing for Wet Age-related Macular Degeneration: 96-week ALTAIR Results

Masahito Ohji MD

Identifying Ophthalmological Diagnoses and Treatable Diseases by Image-Based Deep Learning

Michael Goldbaum MD MS

Port Delivery System With Ranibizumab (PDS): From Dose Ranging in Ladder Phase 2 to Archway Phase 3 Study Design

Dante Pieramici MD

Subretinal Implantation Of Human Retinal Progenitor Stem Cells (Hrpc) for Retinitis Pigmentosa: Phase I/Ii Interim Safety Results

Jason I Comander MD PhD

OCT-Angiography Results from the PRO-CON Study: Intravitreal Aflibercept Injection (IAI) versus Sham as Prophylaxis against Conversion to Neovascular Age-Related Macular Degeneration (nAMD) in High-Risk Eyes

David M Brown MD

Prediction of Retinal Pigment Epithelial Tears: The True Story

Nicole Eter MD and Christoph Clemens MD

I. Classification of Retinal Pigment Epithelial Detachment (PED)
   A. Drusenoid PED
   B. Serous PED
   C. Serous vascularized PED
   D. Fibrovascular PED

II. Imaging of PED
   A. Color fundus photography
   B. Confocal scanning laser ophthalmoscopy (cSLO) near-infrared reflectance (NIR)
   C. Fundus autofluorescence (FAF)
   D. Fluorescein angiography (FLA)
   E. Indocyanine green angiography (ICG)
   F. Spectral domain OCT (SD-OCT)
   G. OCT angiography (OCT-A)

III. PED and Anti-VEGF

IV. Risk Factors for Pigment Epithelial Tears
   A. PED lesion's height and diameter
   B. Hyper-reflective lines in near-infrared images
   C. Small ratio of CNV size to PED size
   D. Subretinal clefts
   E. Microrips
   F. Duration of PED

V. Mechanism of Pigment Epithelial Tears
   A. Contraction of CNV membranes → shrinkage of the retinal pigment epithelium (RPE) → increased tension on the surface of the cavity
   B. Two opposite forces on the marginal RPE: traction forces from CNV contraction and adhesive forces from the RPE still attached
   C. The contracted RPE monolayer comes to rest on the side of the CNV; the RPE tear appears on the opposite side of CNV

VI. Prediction of Pigment Epithelial Tears
   A. Radial hyper-reflective lines spreading in a funnel-like pattern across the PED lesion in NIR images
   B. Wrinkles in the RPE on SD-OCT

VII. Classification of Pigment Epithelial Tears
   A. Small / large
   B. Central / perifoveal
   C. Unilobular / multilobular

VIII. Treatment Status Post Pigment Epithelial Tear
   A. Observation
   B. Continued anti-VEGF therapy

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Twelve-Month Interim Analysis of a Randomized Clinical Trial of Ranibizumab vs. Aflibercept in Neovascular AMD: The RIVAL Study

Mark C Gillies MD PhD, Alex P Hunyor MB BS, Jennifer J Arnold MB BS(Hons), Robyn H Guymer MB BS PhD, Sebastian Wolf MD PhD, Paul Ng MB BS, Francois L Pecheur PharmD, Ian L McAllister MB BS DM

Introduction

Although they are directed at the same target, the vascular endothelial growth factor (VEGF) inhibitors ranibizumab (RBZ) and aflibercept (AFL) have differences in pharmacological and biologic characteristics that may confer different efficacy and safety profiles when they are used to treat neovascular AMD (nAMD).

The possibility that long-term VEGF inhibition might cause macular atrophy is currently being debated. The SEVEN-UP study reported an overall mean loss of 8.6 letters from baseline after 7 years of treatment with RBZ ($N = 65$), with over 90% reported to have developed macular atrophy.[1] The long-term visual outcomes from the Fight Retinal Blindness (FRB) registry, in which eyes had been treated much more frequently than in SEVEN-UP, reported better outcomes, but there was still a mean loss of 2.6 letters after 7 years of treatment, and 39% of eyes that had a 10-letter loss were reported to have had central macular atrophy.[2]

There are currently no published data on the risk of macular atrophy in eyes receiving treatment with AFL, or any direct comparison between AFL and RBZ and the risk of developing atrophy.

The RIVAL Study

The RIVAL study is a randomized clinical trial (RCT) of 0.5-mg RBZ or 2.0-mg AFL using a reading center–controlled treat-and-extend (T&E) regimen for the treatment of nAMD that was conducted at 24 sites across Australia. The study was designed to investigate whether there is a difference in the risk of developing macular atrophy between RBZ and AFL. The primary endpoint, the mean change in area of macular atrophy from baseline to Month 24, will be reported in the full analysis.

In this presentation we report the results of the preplanned 12-month interim analysis of the mean number of injections and the mean change in BCVA, measured in logMAR letters, from baseline to Month 12, two of the predefined secondary efficacy outcomes of the RIVAL study.

Patients 50 years of age or older presenting with baseline BCVA of 23 letters or more and diagnosed by investigators with active subfoveal choroidal neovascularization (CNV) secondary to nAMD were randomized in a 1:1 ratio to receive either 0.5-mg RBZ or 2.0-mg AFL.

After 3 initial monthly injections, patients followed an individualized T&E regimen, according to the following disease activity criteria:

- Loss of VA of ≥ 5 letters from the best VA recorded since treatment started (nAMD related)
- New retinal hemorrhage
- Any intraretinal fluid (IRF) or subretinal fluid (SRF) on spectral domain OCT

The injection interval was extended by 2-week increments if none of these signs of disease activity were present (maximum of 12-week intervals); otherwise it was kept at 4 weeks. Once extended, the treatment interval had to be reduced by 2-week increments if there was 1 sign of disease activity, or reduced to every 4 weeks (the minimum interval allowed) if there were 2 or more signs of disease activity. Extension occurred again at subsequent visits if there were no signs of disease activity. Investigators were unmasked; however, BCVA assessors and the Central Reading Center that determined the presence of IRF/SRF were masked.

Results From the Preplanned 12-Month Interim Analysis of Prespecified Efficacy Secondary Endpoints

Baseline Characteristics

281 patients were randomized (RBZ, $n = 142$; AFL, $n = 139$). Baseline characteristics of the 2 treatment groups appeared to be similar. The mean baseline BCVA score was 65.0 and 65.2 letters in the RBZ and AFL arms, respectively.

Mean Changes in BCVA and Number of Injections From Baseline to Month 12

278 patients (RBZ, $n = 141$; AFL, $n = 137$) were included in the full analysis set, with a mean BCVA at baseline of 65.3 letters and 65.1 letters in the RBZ and AFL arms, respectively. Thirty patients (10.8%) did not complete the first 12 months of the study (RBZ, $n = 14$ [9.9%]; AFL, $n = 16$ [11.7%]). The mean BCVA of these patients at their last visit (mean change from baseline) was 66.1 letters (+7.1) for the RBZ arm and 64.8 letters (+2.0) for the AFL arm. BCVA in the completers' cohort increased at Month 12 to 72.9 letters ($n = 127$) and 70.5 letters ($n = 121$) in the RBZ and AFL arms, respectively, with a mean change in BCVA of +6.9 letters for the RBZ arm and +5.2 letters for the AFL arm. When using the random effects mixed model with continuous baseline BCVA adjustment, the estimated mean change in BCVA from baseline to Month 12 was +7.2 letters for the RBZ arm and +4.9 letters for the AFL arm. The estimated difference between the 2 treatment arms was 2.3 letters at 12 months ($P = .059$). Similar results were found after performing a sensitivity analysis by imputing data using the last observation carried forward (LOCF) method. The mean number of intravitreal injections from baseline to Month 12 was 9.7 in both arms.

Conclusions

RIVAL, the first RCT to compare RBZ and AFL in nAMD patients when using an identical T&E regimen, found that both RBZ and AFL achieved good visual acuity improvements, requiring the same number of injections, over 12 months. The study primary endpoint (change in area of macular atrophy at 24 months) will be reported in the full study analysis.

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What Is Actually in the Syringe? Accuracy and Precision of Intravitreal Injections of Anti-VEGF Agents in Real Life

Anat Loewenstein MD, Itamar Loewenstein, Michaella Goldstein MD, Joseph Moisseiev MD, Elad Moisseiev MD

Introduction

Intravitreal injection is the most commonly performed procedure in ophthalmology. Many studies have focused on the technical aspects of performing intravitreal injections, but only a few have investigated the accuracy of the intravitreal drug volume delivery of this common procedure. Several studies have shown that the accuracy and reproducibility achieved with the typical syringes used for intravitreal injections can be highly variable. The purpose of this study is to evaluate the accuracy and precision of anti-VEGF volume delivery in the "real-world" setting.

Methods

Volume output was measured in 669 intravitreal injections administered to patients, calculated from the difference in syringe weight before and after expelling the drug. Three groups were included: prefilled bevacizumab in a 1.0-mL syringe (Group 1, $n = 432$), prefilled ranibizumab in a small-volume syringe with low-dead-space plunger design (Group 2, $n = 125$), and aflibercept drawn by the physician from a vial and injected with a 1.0-mL syringe (Group 3, $n = 112$). Accuracy was analyzed by mean absolute percentage error (MAPE), and precision by coefficient of variation (CV).

Results

Volume outputs in all 3 groups were significantly different from the target of 50 µL ($P < .0001$ for all), indicating that in all 3 groups the actually delivered volume outputs are different than those intended. A deviation of more than 10% in volume output was recorded in 60% of the injections. MAPE values were 12.25% ± 5.92% in Group 1, 13.60% ± 8.75% in Group 2, and 24.69% ± 14.84% in Group 3. No difference was found between Groups 1 and 2, but both were significantly more accurate than Group 3 (see Figure 1, $P < .0001$ for both), indicating that prefilled syringes may be associated with improved accuracy of drug delivery. Precision was highest in Group 2 (see Figure 2), indicating that a small-volume syringe with a low-dead-space plunger design may improve precision.

Conclusions

The current practices used for intravitreal injections are highly variable, with significant rates of over- or under-delivery, which may possibly be associated with IOP elevation or undertreatment of patients. This is the first study to investigate the accuracy and precision of anti-VEGF agents delivered by intravitreal injection to patients, and its findings illustrate the need for a specially designed syringe for this purpose. Use of a prefilled syringe was associated with improved accuracy, and a small-volume syringe with a low-dead-space plunger design may improve precision.

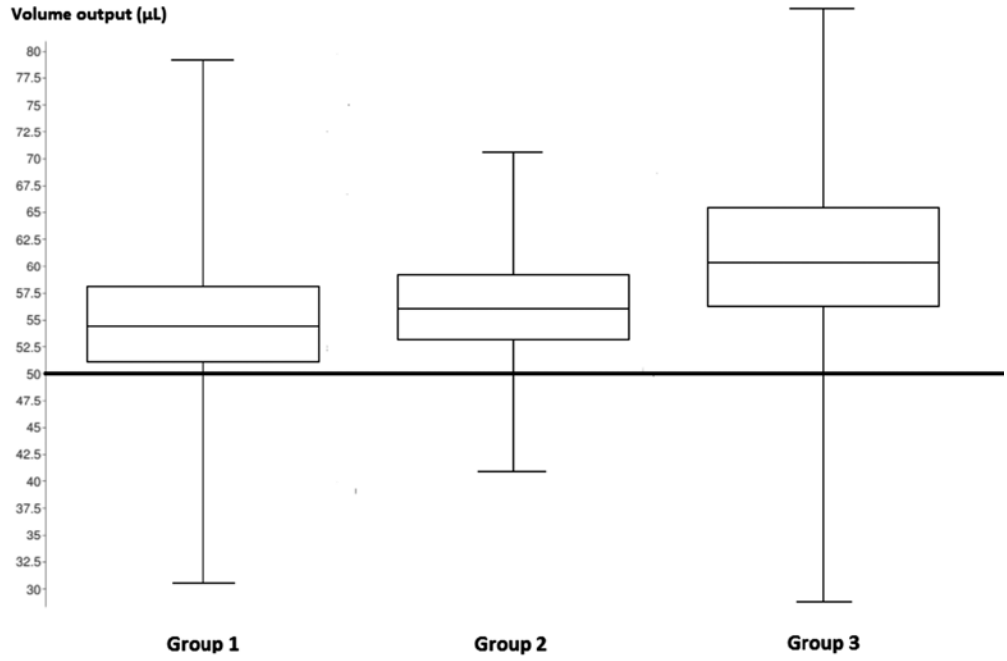

Figure 1. Box-and-whiskers plot showing mean volume output for the 3 groups, compared to the intended volume of 50 µL (bold line).

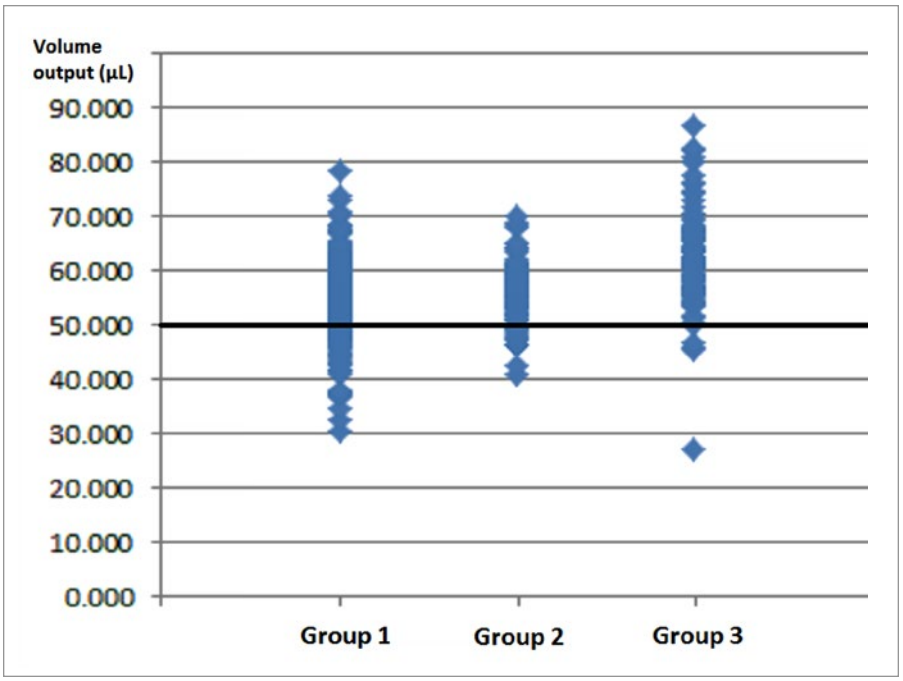

Figure 2: Scatter plot showing distribution of volume outputs measured for each syringe design, compared to the intended volume of 50 µL (bold line).

Histopathology of Macular Neovascularization

David Wilson MD

Definition

In AMD, neovascularization can be defined as growth of blood vessels into a location that is normally devoid of blood vessels, or the growth of blood vessels in a manner that gives them abnormal morphologic or physiologic features. The most pertinent abnormal features are a structure that permits leakage of fluid through the wall of the vessel, or one that allows hemorrhage into adjacent tissue.

Histopathology

Outer Retina

Neovascularization in the outer retina has been referred to as type 3 neovascularization, and retinal angiomatous proliferation (RAP). This type of neovascularization often produces adjacent retinal edema and small intraretinal hemorrhages. It is frequently accompanied by an adjacent retinal pigment epithelial (RPE) defect and serous pigment epithelial detachment. On fluorescein angiography, the neovascularization appears as a punctate area of hyperfluorescence with leakage in the later frames of the angiogram. Histologically the neovascularization consists of a small complex of capillary-sized vascular channels surrounded by a fibrous matrix. There are generally RPE cells that have migrated into the retina and surround the neovascular complex. The neovascular complex rests against the Bruch membrane, and in many cases there is an associated serous pigment epithelial detachment.

Between the Photoreceptors and RPE

Neovascularization in this potential space has been referred to as type 2 neovascularization. This type of neovascularization almost always produces a serous detachment of the retina and is also associated with subretinal hemorrhage. On fluorescein angiogram it has the appearance of classic choroidal neovascularization. There is generally a branching or cartwheel network of vessels, with prominent leakage in the late frames of the angiogram. Histologic examination reveals vessels within the space between the RPE and photoreceptors. There is generally proteinaceous fluid present in the subretinal space, with surrounding loose collagenous tissue. There is a variable amount of loose RPE cells and fibroblast-like cells.

Within the Bruch Membrane

Neovascularization beneath the RPE layer and anterior to the elastic portion of the Bruch membrane has been referred to as type 3 neovascularization. This is the most common location for neovascularization in AMD. Neovascularization in this location is associated with a variety of phenotypes. The most characteristic finding is a fibrovascular pigment epithelial detachment, in which there is stippled hyperfluorescence of the shallow RPE elevation on fluorescein angiography. There is generally gradual leakage in the late frames of the angiogram. Shallow subretinal fluid is generally present. Exudative findings do not always accompany type 1 neovascularization, and the recently described nonexudative neovascularization is really a subtype of type 1 neovascularization. On histologic examination, the overlying RPE is relatively intact. In most instances, there is a prominent layer of basal laminar deposit beneath the RPE. The fine blood vessels are located beneath the basal laminar deposits and the elastic portion of the Bruch membrane. In fact, the blood vessels are probably in this location due to a pathophysiologic cleavage plane that has developed between the basal laminar deposit and the elastic portion of the Bruch membrane. The vessels are fed from the choroidal circulation by vessels that penetrate from the underlying choroidal circulation. The vessels that comprise type 1 neovascularization exist in a very prominent fibrocellular matrix. So it is really more accurate to think of type 1 neovascularization as a tissue layer. It will not completely disappear with treatment of the blood vessels with antiangiogenic agents.

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Influence of Choroidal Thickness on Drusen and Exudative AMD Subphenotype

Gemmy Chui Ming Cheung MB BChir FRCOphth

We evaluated the association between choroidal thickness and the characteristics of drusen and exudative AMD subphenotypes in 145 Asian patients and 214 white patients. Drusen were graded into 3 subtypes (pachydrusen, soft drusen, and pseudodrusen) based on color fundus photographs. Subfoveal CT was measured using spectral domain OCT. In patients with exudative AMD in their fellow eyes, the lesions were classified into polypoidal choroidal vasculopathy (PCV), choroidal neovascularization (CNV), or type 3 neovascularization.

The Asian cohort had significantly higher prevalence of pachydrusen (25.5% vs. 8.4%, $P < .001$) and PCV (46.9% vs. 0%, $P < .001$), compared to the white cohort. Eyes with thicker choroid (≥ 250 μm) were more likely to have pachydrusen than soft drusen or pseudodrusen in both cohorts (62.2% vs. 31.3% vs. 8.0%, $P < .001$ from the Asian cohort; 94.4% vs. 37.8% vs. 18.8%, $P < .001$ from the white cohort); this association remained significant after adjusting for age, gender, and fellow eye neovascularization subphenotype (OR 1.06; 95% CI, 1.01-1.11; $P = .026$ in the Asian cohort and OR 1.08; 95% CI, 1.04-1.13; $P < .001$ in the white cohort). In the Asian cohort, patients with PCV were more likely to have thicker choroid ($P = .041$) and pachydrusen ($P < .001$ compared to pseudodrusen, $P = .039$ compared to soft drusen). These results demonstrate choroidal thickness is independently associated with drusen subtype, and support the hypothesis that choroidal thickness may modulate disease manifestation in AMD.

Brolucizumab: Will It Make a Difference?

Andrew P Schachat MD

I. What Is Brolucizumab?

A. Brolucizumab is currently being studied for the treatment of wet AMD. It has previously been referred to as "RTH258" and "ESBA1008."

B. It is a humanized microfusion protein with the complementarity-determining regions (CDRs) of VEGF-A.

C. The drug is a relatively small molecule with potent inhibition of and high affinity to all VEGF-A isoforms. In preclinical studies, brolucizumab inhibited activation of VEGF receptors apparently through prevention of the ligand-receptor interaction.[1]

II. Why Might It Represent a Step Forward in Anti-VEGF Therapy?

The drug is significantly smaller than other anti-VEGF agents.

Bevacizumab is about 150 kilodaltons (KD), aflibercept is about 100 KD, and ranibizumab is about 50 KD, whereas brolucizumab is about 26 KD. Compared to the 0.5-mg ranibizumab dose, a 6.0-mg dose of brolucizumab represents 22x more molar concentration. Broluciuzmab has a higher binding affinity than ranibizumab, which would presumably allow it to last longer in the eye and, in theory, permit less frequent dosing. The dosing interval is being studied in clinical trials.

III. Summary of Clinical Trial Data

A. Phase 1/2: Six-month trial, 194 subjects, RTH258 compared to ranibizumab[2]

The primary efficacy endpoint was the change from baseline to Month 1 in central subfield thickness (CSFT) measured by spectral domain OCT. The CSFT was noninferior to ranibizumab for the 4.5- and 6.0-mg doses (but not the lower doses).

B. Phase 2: Three- to 4-month trial, 89 subjects, brolucizumab vs. aflibercept[3]

Primary outcome, noninferiority (5 letter margin) in BCVA. The primary outcome was met at both 12 and 16 weeks with no notable differences up to Week 40.

C. Phase 3: Presented but not yet published. Pair of randomized clinical trials (RCTs) called HAWK and HARRIER.

1. Basic design: Brolucizumab vs. aflibercept

a. 3.0-mg and 6.0-mg brolucizumab doses vs. 2.0-mg aflibercept

b. Three monthly loading doses and then every 8 weeks aflibercept and every 12 weeks brolucizumab arms

c. If there was evidence of disease activity in the brolucizumab arms, then the dosing interval was decreased to every 8 weeks. There was no mechanism to decrease dosing frequency once reduced to every 8 weeks.

2. Primary outcome: Noninferiority of brolucizumab to aflibercept in mean change in BCVA from baseline to Week 48.

The noninferiority margin is 4.0 letters (about 1 line on the chart).

3. In HAWK, 52% on 3-mg brolucizumab and 57% on 6-mg brolucizumab were maintained on every-12-weeks dosing following the loading phase. In HARRIER, 52% of patients on brolucizumab were still on an every-12-weeks interval at Week 48.[4,5]

4. Safety: The overall safety of brolucizumab appears to be comparable to that of aflibercept and consistent with that of other anti-VEGF drugs.

IV. Brolucizumab clinical trials appear to show that it is noninferior to aflibercept at 1 year with an increased dosing interval.

V. How to Decide if a New Drug "Will Make a Difference?"

A. Better efficacy?

1. Can't claim better efficacy ("superiority") but can assert noninferiority to aflibercept. The noninferiority margin is reasonable, 4 letters. When considering "efficacy creep" as we interpret noninferiority trials, brolucizumab appears to be within about a line on the letter chart as effective as aflibercept.

2. What primary outcome is being looked at? Mean change in BCVA at about a year (48 weeks). This is a clinically meaningful outcome that would matter to patients.

3. Brolucizumab and aflibercept could only be directly compared up to Week 16 because thereafter the dosing interval differed. At this time point, there is a suggestion that brolucizumab dries the retina better on OCT. Future evaluations will test whether this is true.

B. Better safety?

Probably similar. Larger studies with longer follow-up are needed to see if differences become apparent. For now, safety seems equivalent to the other marketed anti-VEGF drugs.

C. Reduced treatment burden or "more convenient?"

Yes, but not a lot. Noninferior outcomes were achieved with approximately 1 fewer injection in Year 1. After the initial monthly loading dose phase, somewhat more than 50% of subjects could be maintained on a 3-month dosing schedule at Week 48. Compared to aflibercept label dosing[6] (monthly for 3 months and then every 8 weeks, so about 7.5 doses per year), brolucizumab monthly for 3 doses and then every 3 months achieves a noninferior acuity outcome, with about 6 doses a year. If the benefit is maintained with longer treatment, which is not known yet, the convenience or reduced treatment burden grows over time. Keep in mind that the 3-month dosing was not achieved in somewhat less than half of study subjects, so presumably they will receive about the same number of injections as aflibercept-treated patients.

D. Less costly? Not yet known. If the drug is priced well under the cost of aflibercept or ranibizumab, that would be a significant benefit.

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Oncology Panel

Panel Moderator: Prithvi Mruthyunjaya MD

Panelists: David H Abramson MD FACS, Colleen M Cebulla MD PhD, Evangelos S Gragoudas MD, Tara A McCannel MD, Timothy G Murray MD MBA, Amy C Schefler MD

NOTES

Lessons Learned From DRCR Protocols I, S, T, and U: New Treatment Paradigms for DME and PDR

John A Wells III MD

Anti-VEGF therapy is now the mainstay of treatment of diabetic macular edema (DME) and is a valid alternative to panretinal photocoagulation (PRP) for proliferative diabetic retinopathy (PDR). I will review how results from Diabetic Retinopathy Clinical Research Network (DRCR.net) studies led to these changes in treatment paradigms.

Protocol I

Protocol I evaluated 4 treatments for eyes with center-involved DME: (1) ranibizumab 0.5 mg with prompt laser, (2) ranibizumab 0.5 mg with laser deferred for 6 months, (3) triamcinolone 4 mg with prompt laser, and (4) prompt laser with sham injection. The results were the first to demonstrate the superiority of anti-VEGF therapy over focal laser for DME.

The outcomes that most inform clinical practice are as follows:

1. At 2 years, ranibizumab, with prompt or deferred laser, is superior to triamcinolone + focal laser or focal laser alone (+7, +10, and +2 letters gained, respectively).
2. Ranibizumab, with prompt or deferred laser, and triamcinolone + laser *are* equally effective in pseudophakic eyes (+8, +8, +7 letters gained at 1 year), but glaucoma risk limits its use.
3. Deferral of laser for 6 months may result in better 2- and 5-year VA outcomes, especially in eyes with 20/50 or worse baseline vision,
4. Ranibizumab treatment burden declines over 5 years (median: 8-9 injections Year 1, 2-3 injections Year 2, 1-2 injections Year 3, 0-1 injections Year 4, 0 injections Year 5).

Protocol T

Protocol T compared 3 anti-VEGF agents for the treatment of center-involved DME: aflibercept 2 mg, bevacizumab 1.25 mg, and ranibizumab 0.3 mg. Two-year outcomes were dependent on a prespecified subgroup analysis of better or worse baseline vision: (1) in eyes with baseline vision 20/32-20/40, mean VA gain of +8 letters with all 3 agents, (2) in eyes with baseline vision 20/50 or worse, mean VA gain with aflibercept of +18 letters, equivalent to ranibizumab +16 letters but superior to bevacizumab, +13 letters; (3) however, an area under the curve analysis favored aflibercept over 2 years in worse baseline VA eyes, and (4) in worse baseline vision eyes, there were more 3-line gainers with aflibercept at 1 year, but there was equivalency with all 3 agents at the 2-year end point.

Important outcomes independent of baseline vision include the following:

1. The treatment burden is equal with all 3 agents: 15-16 injections through 2 years (9-10 in Year 1, 5-6 in Year 2).
2. Bevacizumab reduces OCT thickness about 40%-50% less than ranibizumab and aflibercept.
3. Laser treatment is given more often to bevacizumab-treated eyes because these eyes have less reduction in OCT thickness.

A separate subgroup analysis of vision outcomes at 1 year combining the prespecified baseline vision subgroups and OCT thickness greater or less than 400 microns showed that: (1) in worse baseline vision eyes, aflibercept is superior regardless of baseline OCT thickness and (2) in the better baseline VA subgroup, there were superior vision outcomes with aflibercept or ranibizumab over bevacizumab when OCT thickness was greater than 400 microns.

Finally, Protocol T showed that through 1 year, bevacizumab-treated eyes had less improvement in retinopathy severity compared to aflibercept and ranibizumab, but rates of worsening of retinopathy were similarly low with all 3 agents.

Protocol S

Protocol S compared PRP to ranibizumab 0.5 mg for the treatment of PDR. However, in eyes with PDR and center-involved DME, ranibizumab 0.5 mg treatment was also given in the PRP group.

Two-year results showed that eyes with PDR and coexisting DME gained more vision if treated with ranibizumab alone than did eyes treated with ranibizumab + PRP (+8 vs. +2 letters), whereas eyes with PDR and no DME at baseline had similar vision outcomes regardless of treatment (+1.8 vs. −0.5 letters, respectively). However, an additional benefit of ranibizumab monotherapy was dramatically less visual field loss compared to eyes treated with PRP. Additionally, ranibizumab monotherapy eyes had lower rates of vitrectomy, vitreous hemorrhage, and progression to traction retinal detachment than the PRP group.

Protocol U

Protocol U studied eyes with persistent center-involved DME after 6 months of anti-VEGF monotherapy and randomized eyes to ranibizumab 0.3 mg monthly monotherapy or ranibizumab 0.3 mg monthly + dexamethasone 0.7-mg implant every 3 months.

At 6 months, mean VA improvement by 6 was no better in the dexamethasone + ranibizumab group than in the sham + ranibizumab group (mean gain: +2.7 vs. +3.0 letters, respectively). Adding dexamethasone did not reduce the number of ranibizumab injections in this short-term study. On average, there was a greater reduction in retinal thickness in the dexamethasone + ranibizumab group than the ranibizumab group (–110 microns vs. –62 microns). As expected, more eyes in the dexamethasone + ranibizumab group experienced elevations of IOP (29% vs. 0%). While pseudophakic eyes did better with the combination group than phakic eyes did, the study was not sufficiently sized to determine whether treatment response might differ by lens status.

In summary, DRCR protocols have clarified many issues in the treatment of center-involved DME. I believe that numerous guidelines can be gleaned from the results of Protocols I, T, S, and U:

1. Treatment should be initiated with anti-VEGF therapy, and focal / grid laser should be deferred for 6 months.
2. Aflibercept should be the initial choice when baseline VA is 20/50 or worse.
3. Aflibercept, bevacizumab, or ranibizumab can be given in eyes with baseline VA 20/32 to 20/40, recognizing however that bevacizumab reduces OCT edema less effectively and is more likely to result in persistent DME.
4. The number of injections required to treat DME declines over time.
5. In eyes with PDR and coexisting DME, ranibizumab treatment alone should be considered over PRP + ranibizumab.
6. In eyes with persistent DME after at least 6 months of anti-VEGF therapy, continuing anti-VEGF monotherapy can result in continued improvement, and adding triamcinolone does not result in better vision outcomes in the short term, while increasing glaucoma risk.
7. Anti-VEGF therapy with any of the available agents can improve retinopathy severity in a substantial percentage of patients, appears to greatly reduce the risk of retinopathy worsening, and should be considered for eyes with severe nonproliferative PDR.

Can We Confidently Predict 2-Year Outcomes in a Patient Following 3 Anti-VEGF Injections for Diabetic Macular Edema?

Neil M Bressler MD

Adapted from Association of early response to anti-VEGF injections with two-year outcomes among eyes with diabetic macular edema in protocol T. Am J Ophthalmol. *In press.*

I. Background

A. Analysis of DRCR Network Protocol I data showed a strong relationship between 12-week change in visual acuity and 1- and 3-year changes in VA among eyes treated with ranibizumab for diabetic macular edema (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 mean visual acuity 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 (dexamethasone + ranibizumab).

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.

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Five-Year Outcomes for Changes in Diabetic Retinopathy Severity When Treating Diabetic Macula Edema With Ranibizumab: DRCR.net Protocol I

Susan B Bressler MD

Introduction

Multiple randomized clinical trials evaluating anti-vascular endothelial growth factor (anti-VEGF) therapy in eyes with diabetic macular edema (DME) have demonstrated that some eyes simultaneously experience favorable alterations in retinopathy severity. Protocol I, conducted by the Diabetic Retinopathy Clinical Research Network (DRCR.net), evaluated ranibizumab with prompt or deferred focal / grid photocoagulation in eyes with center-involved DME and vision impairment (Snellen equivalent 20/32 to 20/320). Eyes assigned to ranibizumab in this randomized clinical trial were managed with a structured retreatment algorithm based on evolution of visual acuity and central subfield thickness (CSF) measurements from OCT images obtained according to standardized protocols. Participants were followed for up to 5 years. With adherence to the retreatment protocol, the frequency of ranibizumab administration decreased with each successive year of study follow-up. As such, the database from Protocol I provides an opportunity to explore the changes in diabetic retinopathy severity that occurred in eyes managed with ranibizumab for DME over a longer period of follow-up (5 years), and specifically in the setting in which drug exposure was reduced in the later years of the study.

Methods

Diabetic retinopathy severity (DRS) was assessed from study visits and annual fundus photographs read by an independent reading center. The proportion of eyes that improved at annual examinations and the cumulative probability of worsening through 5 years were estimated. Improvement was defined as absence of (a) panretinal photocoagulation (PRP), vitrectomy, or anti-VEGF injection to manage proliferative diabetic retinopathy (PDR) or its complications and no vitreous hemorrhage, retinal detachment, anterior segment neovascularization, or neovascular glaucoma, and (b) at least a 2-step regression of DRS level on the photographs relative to baseline when applying the ETDRS DRS scale. Worsening was reflected by report of any of the events described in "a" above, at least a 2-step progression of DRS level on the photographs, or worsening from no PDR to PDR (≤ level 53 progressing to level 60 or higher).

Results

At baseline, 235 participants had non-PDR (NPDR), among which 29%, 28%, and 32% of eyes had retinopathy improvement at 1, 3, and 5 years, respectively. For the 111 participants with PDR at baseline, the corresponding percentages demonstrating improvement were 38%, 35%, and 23%. The cumulative probability of worsening by the 5-year examination was 18% among NPDR eyes (95% CI, 14%-25%) and 31% among PDR eyes (95% CI, 23%-42%; $P = .01$). The mean (SD) number of ranibizumab injections in Years 1, 3, and 5, was 8.1 (2.5), 2.2 (2.6), and 1.8 (2.6) for NPDR eyes, and 9.0 (2.8), 2.3 (2.9), and 1.7 (2.6) for PDR eyes. Proportions of study eyes with DRS improvement or rates of retinopathy worsening did not change with time.

Conclusions

Ranibizumab therapy for DME may be associated with simultaneous favorable changes in DRS throughout a 5-year period, despite sequential reduction in anti-VEGF therapy. The study design of Protocol I does not provide a means to identify the optimal number of anti-VEGF injections to achieve or sustain DR improvement or to evaluate the effect that alterations in DRS may have on vision outcomes.

Regression of Diabetic Retinopathy With Anti-VEGF Treatment: Meta-analysis of 4 Pivotal Clinical Trials

Quan Dong Nguyen MD, Bann-mo Day PhD, Tatiana Ecoiffier PhD, and Ivo Stoilov MD

I. Background

A. Diabetic retinopathy (DR), the most frequent microvascular complication of diabetes, affects approximately one-third of adults over 40 years of age with diabetes.[1,2]

B. DR is the leading cause of new cases of vision loss and blindness among working-age adults in the United States.[2]

C. Clinical trials have demonstrated that ranibizumab (RBZ) results in rapid and sustained DR improvements, and RBZ was FDA-approved for the treatment of DR both with and without diabetic macular edema (DME).[3]

D. The purpose of this study was to conduct a meta-analysis of the effects of RBZ on reducing DR severity in eyes with varying stages of DR and to investigate how anti-VEGF treatment at earlier stages of DR might decrease the risk of vision-threatening PDR.

II. Methods

A. Meta-analysis of randomized controlled clinical trials involving RBZ in eyes with DR (with and without DME): RIDE/RISE and DRCR Protocols I and T.[4-8]

1. Patient level data from RIDE/RISE and DRCR Protocols I and T
2. This meta-analysis reports only the RBZ arm and Sham arms.
3. The RBZ arm is combined 0.3-mg RBZ, 0.5-mg RBZ, 0.5-mg RBZ + Prompt Laser, and 0.5-mg RBZ + Deferred Laser; the Sham arm is included in the "Sham" in RIDE/RISE and the "Sham+Laser" in Protocol I.
4. Patients with prior panretinal photocoagulation (PRP) at baseline were excluded from this analysis.

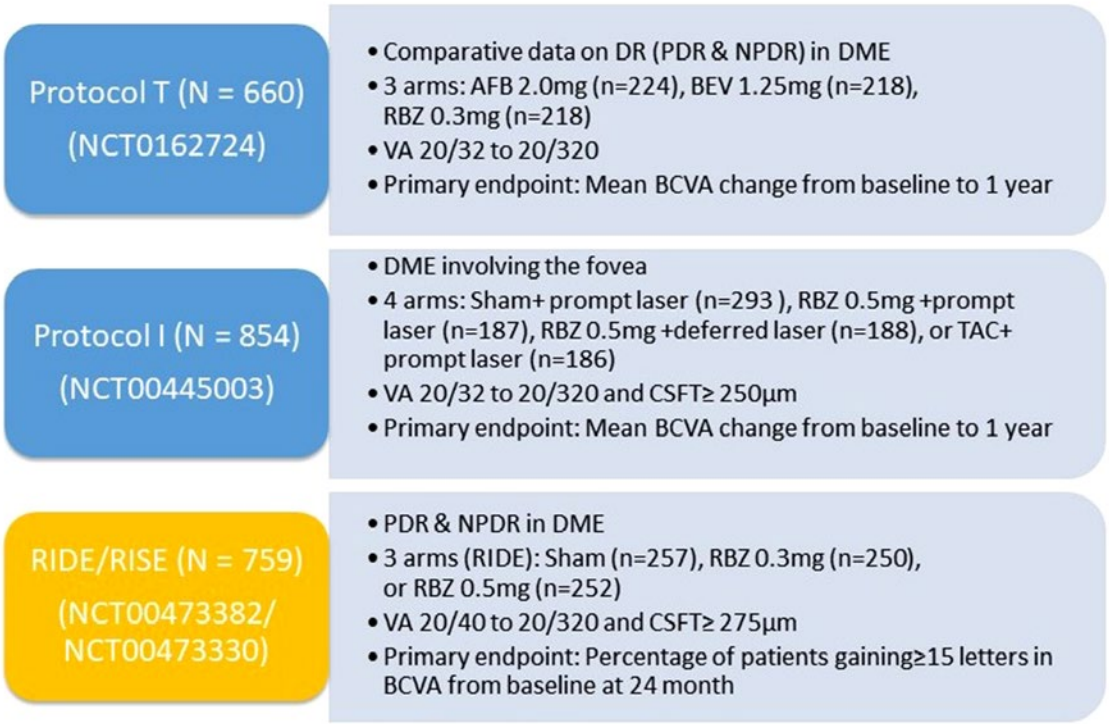

Figure 1. Study designs of the 4 studies in this meta-analysis. Abbreviations: AFB, aflibercept; BEV, bevacizumab; CSFT, central subfield thickness; DME, diabetic macular edema; DR, diabetic retinopathy; NPDR, nonproliferative DR; PDR, proliferative DR; RBZ, ranibizumab; TAC, triamcinolone; VA, visual acuity.

B. Analysis plan

The endpoint: At least 2-step improvements from baseline at Year 1 and Year 2 in observed cases and in last observation carried forward (LOCF) method.

1. By treatment arm (RBZ, Sham)
2. By baseline DR Severity Scale (DRSS) category: Moderate Nonproliferative DR (NPDR; ≤ 43), Moderate to Severe NPDR (47-53), proliferative DR (PDR; ≥ 60)

III. Results

A. A total of 868 RBZ-treated eyes and 439 sham eyes were included in the analysis (see Table 1).

B. Baseline patient characteristics were similar across the 2 treatment arms; distribution of patients by baseline DRSS and BCVA were also comparable (see Table 2).

C. In the overall population, treatment with RBZ resulted in ≥ 2-step improvement in DRSS in over one-third of the patients at both Year 1 and Year 2 in observed cases. Results were similar using the LOCF method.

Table 1. Sample Sizes in the 4 Clinical Trials

	Protocol T (*n* = 553)	Protocol I (*n* = 668)	RIDE / RISE (*n* = 598)	Pooled (*N* = 1819)
Sham			205	439 (24%)
Sham + Prompt Laser		234		
RBZ 0.3 mg	183		197	
RBZ 0.5 mg			196	
RBZ 0.5 mg + Prompt Laser		140		868 (48%)
RBZ 0.5 mg + Deferred Laser		152		
TAC + Prompt Laser		142		142 (8%)
AFB 2 mg	192			192 (11%)
BEV 1.25 mg	178			178 (10%)

Patients with prior panretinal photocoagulation at baseline were excluded.
Abbreviations: RBZ, ranibizumab; TAC, triamcinolone; AFB, aflibercept; BEV, bevacizumab.

Table 2. Baseline Patient and Ocular Characteristics by Treatment Group

	RBZ (*n* = 868)	Sham (*n* = 439)
Female: *n* (%)	371 (43%)	193 (44%)
Age (yrs), *n*	868	439
Mean (SD)	61.8 (10.2)	63.1 (10.2)
Duration of diabetes (yrs), *n*	849	428
Mean (SD)	16.0 (9.2)	15.4 (9.5)
HbA1c, *n*	844	422
Mean (SD)	7.8 (1.6)	7.7 (1.5)
BCVA Mean (SD)	60.8 (12.0)	60.1 (11.7)
DRSS at Baseline, *n* (%)	**RBZ (*n* = 833)**	**Sham (*n* = 412)**
Moderate NPDR (≤ 43)	330 (40%)	141 (34%)
Moderate to Severe NPDR (47-53)	390 (47%)	213 (52%)
Above Mild PDR (≥ 60)	113 (14%)	58 (14%)

Abbreviations: RBZ, ranibizumab; HbA1C, glycated hemoglobin; DRSS, Diabetic Retinopathy Severity Scale; NPDR, nonproliferative DR; PDR, proliferative DR.

Table 3. Improvement of ≥ 2 Steps in DRSS at Year 1 and Year 2

Observed Cases			LOCR		
DRSS ≥ 2-step improvement	RBZ (*n* = 868)	Sham (*n* = 439)	DRSS ≥ 2-Step Improvement	RBZ (*n* = 868)	Sham (*n* = 439)
Year 1, *n*	709	344	Year 1, *n*	769	382
Yes	261 (37%)	22 (6%)	Yes	278 (36%)	23 (6%)
No	448 (63%)	322 (94%)	No	491 (64%)	359 (94%)
Year 2, *n*	453	151	Year 2, *n*	745	383
Yes	197 (43%)	13 (9%)	Yes	258 (35%)	31 (8%)
No	256 (57%)	138 (91%)	No	487 (65%)	352 (92%)

Abbreviations: LOCR, last observation carried forward; DRSS, Diabetic Retinopathy Severity Scale; RBZ, ranibizumab.

Table 4. Improvement of ≥ 2 Steps at Year 1 and Year 2 in Patients With Moderately Severe to Severe NPDR at Baseline (DRSS = 47/53)

Observed Cases			LOCR		
DRSS ≥ 2-step improvement	RBZ	Sham	DRSS ≥ 2-step improvement	RBZ	Sham
Year 1, *n*	328	182	Year 1, *n*	359	200
Yes	205 (63%)	9 (5%)	Yes	220 (61%)	9 (5%)
No	123 (38%)	173 (95%)	No	139 (39%)	191 (96%)
Year 2, *n*	203	69	Year 2, *n*	349	201
Yes	149 (73%)	10 (14%)	Yes	200 (57%)	19 (9%)
No	54 (27%)	59 (86%)	No	149 (43%)	182 (91%)

Abbreviations: LOCR, last observation carried forward; DRSS, Diabetic Retinopathy Severity Scale; RBZ, ranibizumab.

D. Treatment with RBZ resulted in ≥ 2-step improvement in DRSS at both Year 1 and Year 2, and across all baseline DRSS groups in observed cases and using the LOCF method.

E. When patients were stratified by baseline DR severity, the highest rates of DR improvement were observed in the moderately severe / severe NPDR group, with 63% and 73% of these patients showing significant ≥ 2-step improvement at Year 1 and Year 2, respectively. Findings were similar using the LOCF method.

IV. Conclusion

A. Key findings

1. In this meta-analysis of 4 pivotal clinical trials of anti-VEGF treatments for DME, RBZ significantly improved DR in patients with moderate-severe NPDR.

2. Treatment of earlier stages of DR with intravitreal VEGF inhibitors should be considered to prevent development of vision-threatening PDR.

B. Study strengths

Large and diverse patient populations, with > 800 RBZ patients enrolled across all trials

C. Study limitations

1. Studies initiated in different years

2. Inclusion / exclusion criteria were different.

3. Differences in technology and standard practices, and in analyses methods

4. DR was a secondary / exploratory endpoint in these trials.

Disclaimer

The source of the data is the DRCR.net, but the analyses, content, and conclusions presented herein are solely the responsibility of the authors and have not been reviewed or approved by DRCR.net.

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Protocol S: Five-Year Data

Jeffrey G Gross MD

The primary purpose of this randomized clinical trial is to compare visual acuity, rates of diabetic macular edema development, visual field loss, and diabetic retinopathy changes at 5 years in eyes with proliferative diabetic retinopathy receiving intravitreous ranibizumab with deferred panretinal photocoagulation (PRP), if needed, compared with those eyes that receive standard prompt PRP.

At 56 sites in the Diabetic Retinopathy Clinical Research Network (DRCR.net), 394 eyes of 305 adults with proliferative diabetic retinopathy and no prior PRP were assigned randomly to prompt PRP or a standardized treatment protocol of 0.5-mg intravitreous ranibizumab with deferred PRP if needed. Eligible eyes had visual acuity equivalent to Snellen of 20/320 or better. Eyes with or without diabetic macular edema could be eligible but could not have had intravitreous anti-VEGF within 2 months or intravitreous or peribulbar steroids within 4 months of enrollment. Follow-up visits were every 4 weeks to 16 weeks, depending on treatment group and treatment course, for a total of 5 years.

The 2-year outcomes of this study demonstrated that intravitreous ranibizumab was noninferior to prompt PRP for change in visual acuity at 2 years and resulted in superior visual outcomes over the course of 2 years (area under the curve analysis [AUC]) and fewer complications. Final outcomes will include visual acuity at 5 years, AUC visual outcomes over 5 years, proportion of eyes in the deferred PRP group requiring PRP treatment, need for supplemental PRP after completion of initial PRP, need for vitrectomy, frequency of vitreous hemorrhage, frequency of cystoid macular edema development, and treatment frequency in the ranibizumab group to assess durability of anti-VEGF monotherapy for PDR. The 5-year outcomes of this clinical trial will be presented.

Selected Readings

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What Happens to Patients After They Leave DRCR Network Studies?

David Browning MD PhD

Prospective, randomized, controlled clinical trials (RCTs) provide the highest quality evidence for judging the efficacy of interventions. However, RCTs do not address the effectiveness of interventions—that is, the outcomes observed when the interventions are applied under real-world conditions. Published real-world outcomes lag behind those reported in RCTs.[1-4] Strategies to close the efficacy–effectiveness gap are an unmet need in ophthalmology.

The Diabetic Retinopathy Clinical Research Network (DRCR Network) has performed many RCTs for treatments of center-involved, sight-impairing diabetic macular edema (DME). These studies have changed the way we treat DME based on demonstrated efficacy in samples of patients whose characteristics resemble those in seen in practice across the United States. However, the characteristics of care, follow-up, and outcomes after the enrolled patients complete the protocols have not been studied. The goal of this study was to examine what happened to patients in Protocols B, I, and T at one high-enrolling site after the studies were completed.

Protocol B compared serial intravitreal injections of triamcinolone (IVTA) to focal laser (F); the primary outcome was at 2 years. Protocol I compared 0.5-mg intravitreal ranibizumab (IVR) with prompt F, 0.5-mg IVR with deferred F, 4-mg IVTA with prompt F, and sham injection with F; the primary outcome was at 1 year. Protocol T compared serial intravitreal 2-mg aflibercept (IVA), 1.25-mg bevacizumab (IVB), and 0.3-mg ranibizumab (IVR); the primary outcome was at 1 year.

At our site the follow-up during the studies was excellent. Pooling the 3 protocols, retention for the primary outcome visit was 96%. However, when patients left the studies, follow-up fell off. At Years 1, 2, and 3 post-study, the follow-up percentages were 56%, 44%, and 33%, respectively (see Figure 1).

Among the patients who returned after completion of these studies, the median visual acuity improvement was largely retained for Protocols I and T, but it was lost for Protocol B (see Figure 2). The median lessened central subfield thickness was retained for all 3 studies (see Figure 3). It is worth emphasizing that we have no information on the sizable fraction of patients who failed to return.

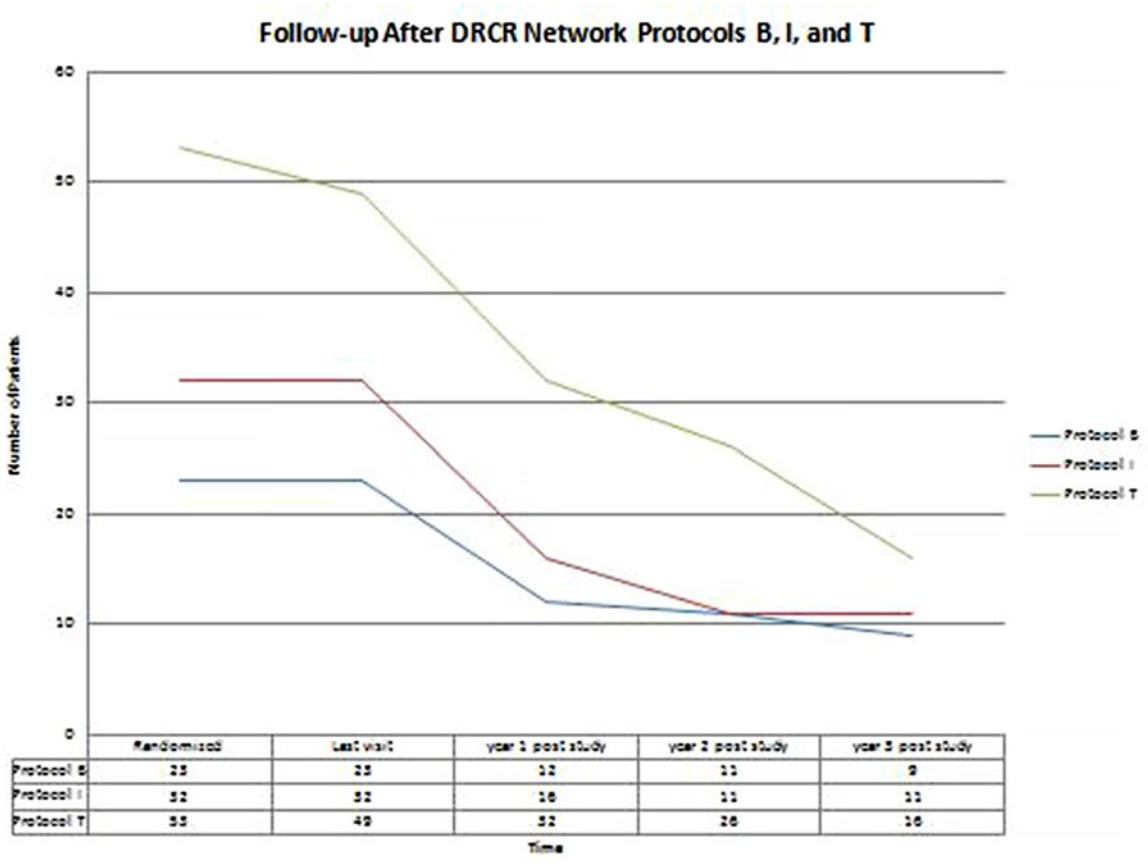

Figure 1.

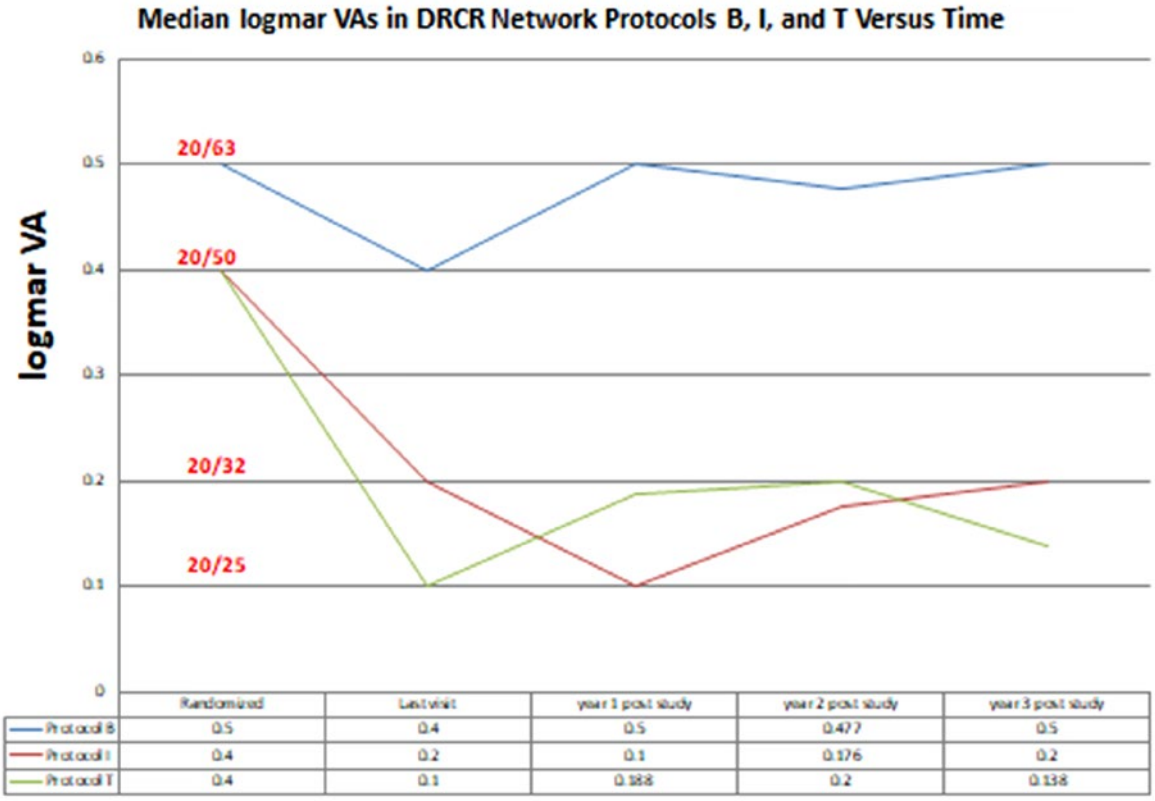

Figure 2.

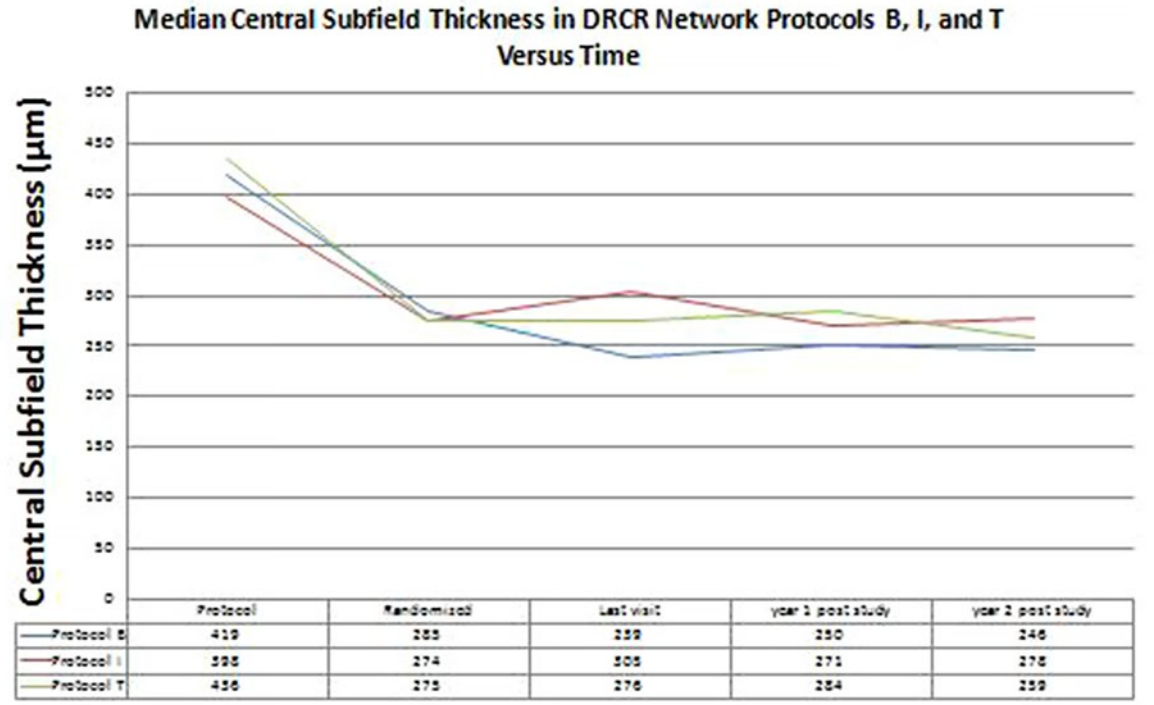

Figure 3.

Follow-up care for patients with DME is important because DME can recur after treatments that lead to initial resolution. But follow-up remains a problem for patients who participate in DRCR Network protocols, as it is for other patients with DME who never are enrolled in RCTs. Some of the features of protocols that boost follow-up within the study, but are lost thereafter, include call-backs by study coordinators who develop personal relationships with the patients, provision of gas cards, and ongoing coaching and education regarding the importance of follow-ups. It might be possible to improve follow-up by making these aspects of care reimbursable under insurance, Medicare, and Medicaid, just as the costs of drugs and labor involved in visits are reimbursable. It is a testable hypothesis, and one worthy of investigation, that reimbursement for these actions would improve effectiveness for treatment of DME and cause it to resemble efficacy. It might be more cost-effective than the current system of care that lacks these features.

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Anti-VEGF Therapy for Proliferative Diabetic Retinopathy: Consequences of Inadvertent Treatment Interruptions

Mark W Johnson MD, Thomas J Wubben MD PhD, and Jason Hsu MD

I. Proliferative Diabetic Retinopathy (PDR) Is Typically a Progressive Disease

Affected eyes are at risk for progression to severe neovascular complications such as traction retinal detachment (TRD) and neovascular glaucoma (NVG) unless:

A. Permanent regression is achieved, or

B. Temporary regression is maintained with ongoing treatment.

II. PDR Regression Following Panretinal Photocoagulation (PRP) Is Highly Durable

A. Long-term follow-up studies and decades of clinical experience demonstrate that once achieved, PRP-induced PDR regression typically lasts indefinitely.

1. Vander and colleagues found that after initial regression of PDR, visual outcome did not vary with length of follow-up.[1]

2. Several investigators have reported that PRP provides good anatomical and visual outcomes for 10 years or longer.[2,3]

3. Blankenship found that PRP provided stable regression for at least 15 years, with only 4% of patients requiring additional laser treatment.[4]

B. Late complications in eyes with PRP-induced PDR regression are generally those associated with tractional effects of vitreous separation (eg, vitreous hemorrhage) rather than progressive growth of neovascular tissue.[1]

III. PDR Treatment With Anti-VEGF Therapy Alone

A. Intravitreal anti-VEGF treatment performs well within the tightly controlled setting of a clinical trial. Treatment with ranibizumab was noninferior to PRP at 2 years in the DRCR Protocol S Trial.[5]

B. The durability of improvements in diabetic retinopathy severity with anti-VEGF treatment ("disease modification")[6] remains unknown.

C. Tadayoni and colleagues reported that despite improvement in clinical features of retinopathy, the area of retinal nonperfusion remained unchanged (69%) or continued to worsen (31%) in eyes receiving monthly anti-VEGF injections (Macula Society 2018).

D. Analysis of Protocol S data suggests that 85% of ranibizumab-treated eyes needed reinjection after a period of treatment withholding (Jennifer Sun, Macula Society 2018).

E. Thus, anti-VEGF therapy for PDR must be regarded as an approach that requires ongoing, possibly perpetual treatment.

F. In the real world, diabetic patients are prone to significant losses to follow-up owing to unanticipated health issues, financial hardship, noncompliance, etc.

1. Obeid and colleagues[7] reported loss to follow-up after treatment for PDR in 25.4% of patients over 4 years.

2. Unanticipated events can affect *even the most reliable patients*.

IV. Consequences of Inadvertent Treatment Interruptions

A. Wubben and Johnson (Retina Society, 2018)

1. Methods

a. Retrospective study of 12 eyes of 11 patients treated exclusively with anti-VEGF therapy for diabetic retinopathy and lost to follow-up for ≥ 4 months

b. Indications for treatment

i. PDR + DME (50%)

ii. PDR (25%)

iii. DME (25%)

2. Results

a. Median length of treatment interruption: 12 months (range: 4-25 months)

b. Most common reasons for loss to follow-up

i. intercurrent illness (33%)

ii. patient noncompliance (33%)

iii. financial issues (17%)

c. Complications found at follow-up visit

i. vitreous hemorrhage (8 eyes)

ii. neovascular glaucoma (5 eyes)

iii. traction or traction-rhegmatogenous retinal detachment (5 eyes)

d. Final visual outcome

i. Eleven of 12 eyes (92%) had vision loss of 3 or more Snellen lines.

ii. Six of 12 eyes (50%) had final visual acuity of hand motion or worse.

B. Hsu et al (ARVO 2018)

1. Methods

   Retrospective cohort study of 76 eyes of 59 patients with PDR that received either anti-VEGF therapy or PRP and then were immediately lost to follow-up for > 6 months

2. Results

   a. Mean VA at final visit significantly worsened in the anti-VEGF group (from 20/53 to 20/166, $P = .006$) but remained unchanged in the PRP group (from 20/53 to 20/58, $P = .45$).

   b. Incidence of TRD at final visit was higher in the anti-VEGF group than in the PRP group (10 vs. 1, $P < .001$).

   c. Incidence of iris neovascularization at final visit was higher in the anti-VEGF group than in the PRP group (4 vs. 0, $P = .02$).

V. Conclusions

A. Diabetic patients are subject to significant losses to follow-up because of unanticipated health issues, financial hardship, and/or noncompliance, etc.

B. In patients with ischemic diabetic retinopathy (especially PDR) managed with anti-VEGF therapy alone, unintentional treatment interruptions can result in visually disastrous consequences, including irreversible blindness.

C. Eyes with PDR that receive only anti-VEGF injections demonstrate worse anatomic and functional outcomes after losses to follow-up compared to eyes that receive PRP.

D. The potentially severe consequences of interruptions in anti-VEGF therapy for PDR should be carefully considered when making initial treatment decisions.

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Diabetes Panel Discussion

Panel Moderator: Judy E Kim MD*

Panelists: J Fernando Arevalo MD FACS*, Barbara Ann Blodi MD, Diana V Do MD*, Rishi P Singh MD*, Jennifer K Sun MD*

NOTES

Nano-retina

Marco Zarbin MD PhD FACS

I. Nanotechnology[1]

The creation and use of materials and devices at the size scale of intracellular structures and molecules; involves systems and structures on the order of < 100 nm

II. Artificial Retina: Replace Lost Photoreceptors (PRs)

A. Optogenetics[2-4]

1. Concept: Virus-induced expression of light-activated molecules linked to ion channels in neurons allows the neurons to generate an electrochemical signal when exposed to light.
2. Method of delivery: Either intravitreal injection or subretinal injection, depending on the virus used to deliver the photosensitizer DNA to the target neurons
3. Device: Molecule whose shape changes when exposed to light; this molecule may activate ion channels directly (eg, channelrhodopsin-2) or through second messenger systems (eg, Opto-mGluR6, rhodopsin).
4. Mechanism of action
   a. Light-sensitive ion channels
      i. Prokaryotic photoactivated ion channels: Light induces configuration change that opens ion channel and either depolarizes (channelrhodopsin) or hyperpolarizes (halorhodopsin) the cell; chromophore is covalently linked *trans*-retinal.
      ii. Synthetic light switch: maleimide-azobenzene-glutamate tethered to ionotropic glutamate receptor (LiGluR/MAG); chromophore is azobenzene.
   b. Photopigments that activate ion channels
      i. Synthetic photopigment (Opto-mGluR6): chimeric all-retinal G-protein coupled receptor consisting of light-sensitive domain of melanopsin and intracellular domains of ON-bipolar cell (BPC)-specific metabotropic glutamate receptor
      ii. Human rod opsin
5. Evidence of efficacy: For rhodopsin expression in BPCs—restoration of VEP and light avoidance in rd1 mice
   a. Behavioral response to naturalistic scenes (eg, swooping owl movie)
   b. Responses at irradiances of 10^{12} photons/cm^2/s, which is typical indoor room light and much better than irradiance required to activate microbial opsins (10^{14}-10^{17} photons/cm^2/s), LiGluR / MAG photoswitch (10^{15}-10^{16} photons/cm^2/s), and similar to Opto-mGluR6
6. Potential visual acuity
   a. When human rhodopsin expression is targeted to BPCs in rd1 mice (rd^1-grm6-RHO mice), behavioral response to fast flicker (4, 10 Hz) suggests the animals have good temporal resolution and can detect stimuli as brief as 50 ms.
   b. Depletion of *cis*-retinal as RPE degenerates may lead to requirement of *cis*-retinal supplementation for advanced cases.
7. Reversibility: Presumed irreversible genetic alteration of target cell (eg, retinal ganglion cell (RGC), BPC, and/or PR depending on method of delivery)
8. Clinical trial status:

   GenSight Biologics (NCT03326336): Recombinant adeno-associated viral vector containing optimized channel rhodopsin ChrimsonR-tdTomato gene under control of ubiquitous CAG promoter (rAAV2.7m8-CAG-ChrimsonR-tdTomato) GS030-Medical Device (GS030-MD) - Visual Interface Stimulating Glasses (amplifies the external visual stimulus to the optogenetically engineered retina) for non-syndromic retinitis pigmentosa (Phase 1/2)

B. Photoswitches[5]

1. Concept: Light-stimulated change in configuration (eg, light-induced *trans-cis* transition) causes molecules to block / open native ion channels in neurons when exposed to light.
2. Device: A photochromic ligand that uses an azobenzene photoswitch to enable light-induced isomerization from the *trans* to the *cis* configuration, which alters binding to native ion channels in retinal neurons
3. Method of delivery
   a. Intravitreal injection
   b. Washout is relatively fast; half-life of DAD-induced light sensitivity is 8.8 hours in rd1 mice.

4. Mechanism of action
    a. Diethylamino-azo-diethylamino (DAD), when activated by light (optimal wavelength: 400-480 nm), assumes higher energy *cis* configuration but quickly relaxes to thermodynamically more stable *trans* configuration in the dark, which alters the compound's binding affinity for target ion channels.
    b. Acts primarily by conferring light sensitivity to BPCs in mouse models (eg, the triple knockout model Cnga3$^{-/-}$ Rho$^{-/-}$ Opn4$^{-/-}$ mice) that lacks all native light responses driven by PRs or photosensitive RGCs and exhibits loss of PRs themselves
    c. DAD mediates a transient excitatory (inward) current on BPCs.
    d. DAD only has an effect on retina that has lost PRs; no effect in areas with viable PRs even if those PRs are nonfunctional!
5. Evidence of efficacy
    a. DAD-injected rd1/rd1 Opn4$^{-/-}$ mice show light sensitivity by spending more time in the light vs. the dark (paradoxical response for a nocturnal animal).
    b. Experiments ex vivo demonstrate biological activity in the retina.
6. Potential visual acuity
    a. DAD generates light sensitivity via BPCs, which allows innate signal processing in the retina to occur.
    b. DAD can generate outputs from both ON and OFF RGCs, which might allow one to identify moving patterns and theoretically supports better image resolution (vs. stimulating ON RGCs only).
    c. Stimulation with 30-µm diameter spot increases RGC activity reliably, suggesting that neighboring RGCs can be controlled independently.
    d. Minimum light intensity for triggering RGC response in DAD-treated rd1 retina is 3x10^{13} photons/cm^2, which is similar to that needed for channel rhodopsin and consistent with very bright light.
7. Reversibility: Fully reversible except for staining of the crystalline lens
8. Clinical trial status: None

C. Quantum dots (QDs)[6]
1. Concept
    a. Light generates electric current in nanoscale semiconductor.
    b. Local electrical field stimulates adjacent retinal neurons (eg, by activating voltage-gated ion channels).
2. Method of delivery: Intravitreal injection of colloidal suspension of cadmium-selenium zinc oxide-biotin QDs (~10^{13})
3. Mechanism of action
    a. QDs behave as semiconductors; when light of appropriate energy (determined by the band gap of the semiconductor) strikes semiconductor, a photovoltaic current can be generated.
    b. QDs can be engineered to absorb light in the visible range.
    c. The amount of current generated by each QD is small.
    d. QDs can be targeted to specific cell types by conjugating targeting ligands on their surface (eg, antibodies); depending on the number of QDs, their proximity to the target neuron, and the environment (eg, dielectric constant), they can stimulate neuronal electrical activity.
4. Evidence of efficacy
    a. Transient improvement in scotopic ERG and retinal histology in RCS rats
    b. QDs have potential toxicity (eg, cadmium core is toxic to mitochondria), but it is believed that toxicity can be modulated by the composition of the external shell.
5. Potential visual acuity: Unknown
6. Reversibility: By 2 days, most QDs have crossed the RCS retina and have been taken up by RPE, where they may remain for ~4 months.
7. Clinical trial status: Early phase clinical trial completed (Mexico)

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Gene Therapy

Szilárd Kiss MD

Background

Gene therapy involves the introduction of new genetic material into a target cell. As a reasonably small, self-contained, easily accessible, and relatively immune-privileged organ with a wide range of well-characterized disorders, the eye is an ideal target for gene therapy. The general components of gene therapy include (1) *genetic material*, which consists of the codon-optimized therapeutic transgene along with promoters, enhancers, and inverted repeats that allow tissue specific expression of the transgene product; (2) *delivery vehicle* to introduce genetic material, with viral vectors currently being the most commonly used; and (3) *route of administration*, either via intravitreal or subretinal injection, to target a variety of retinal and choroidal disorders.

Viral vectors—such as adenovirus, adeno-associated virus (AAV), and lentivirus—that serve as the vehicles in the delivery of genetic materials are first modified to remove the pathogenic machinery but maintain the components of cellular and transit to the nucleus. It is in the nucleus that the payload (the inserted transgene) is transcribed into the desired protein. Viral vectors can be engineered to target specific cell types through modification of the viral capsid (eg, AAV8, AAV9, AAV7m8, etc.) or via tissue-specific transgene protomers (eg, rhodopsin promoter for targeting rods).

Gene therapy can be utilized in variety of ways, depending on the disease and its underlying cause. *Gene augmentation*, where a functioning copy of an abnormal gene is delivered to the cell, is utilized for inherited retinal degenerations (IRDs) involving loss-of-function mutations (eg, Leber congenital amaurosis) or for delivering a protein that is not typically made by the target cell (eg, gene therapy for AMD).

In contrast to gene augmentation, *gene inactivation* gene therapy involves the blocking of the expression of harmful genes. This may be most appropriate for gain-of-function IRDs such as rhodopsin (RHO)-linked autosomal dominant retinitis pigmentosa. In order for gene inactivation to restore the normal cellular proteins, it may need to be coupled with gene augmentation to replace the missing gene function.

Gene editing is a third type of gene therapy. Here the target cell DNA is modified to correct specific mutations. Gene editing may be most appropriate for treating IRDs that involve gain-of-function or dominant negative mutations where a specific DNA sequence is edited out of the target cell and replaced by the sequence of a functioning protein. Unlike gene inaction or gene augmentation, gene editing involves a potential heritability of the modified target cell DNA; it can be passed on to your offspring. The CRISPR/Cas9 system has recently gained a lot of notoriety for gene editing. The CRISPR (clustered regularly interspaced short palindromic repeats) and Cas (CRISPR-associated) system functions as a basic acquired immunity in single-celled organisms in that it imparts resistance to foreign genetic material found in invading viruses. The CRISPR/Cas9 system can efficiently and specifically change genes within a variety of cell types. Off-target effects and unwanted mutations elsewhere in the genome of target cells are two important considerations with all gene editing therapeutics.

Gene Therapy for IRDs

Several dozen ocular gene therapy trials have been completed, are currently ongoing, or are in the planning stages and expected to start within the next few years. A great majority of clinical activity in ocular gene therapy has centered on monogenetic IRDs. There are several reasons for this, including the precise identification of the target gene (eg, *CNGA3* and *CNGB3* in the case of achromatopsia) and the clear and relatively straightforward path to U.S. Food and Drug Administration (FDA) approval. The latter is due in part to the fact that IRDs are considered by the FDA to be orphan diseases (that is, they are defined as diseases that affect fewer than 200,000 patients in the United States), and most treatments can gain breakthrough therapy designation. The incentives with orphan product and breakthrough therapy designations include, among other things, a less cumbersome timeline for submission for FDA approval and a potential 7-year exclusivity once a product is FDA approved. With the recent FDA approval in of Luxturna (voretigene neparvovec, Spark Therapeutics), gene augmentation with AAV2-based ocular gene therapy moved from bench to bedside and entered the realm of clinical reality.

RPE65-mediated IRDs

In December 2017, the FDA approved voretigene neparvovec for the treatment of IRDs due to abnormalities in the *RPE65* gene. With this approval, voretigene neparvovec become not only the first gene therapy to be FDA approved but also the first approved pharmacologic treatment for any IRD. Voretigene neparvovec is an AAV-based gene therapy that is delivered into the subretinal space following a pars plana vitrectomy in patients with pathological mutations in both copies of the *RPE65* gene. The *RPE65* gene, expressed in retinal pigment epithelial (RPE) cells, encodes a carotenoid ozygenase enzyme that converts 11-trans-retinyl esters to 11-cis-retinol; this is then used in visual pigment regeneration in photoreceptors. Mutations in *RPE65* have been associated with Leber congenital amaurosis type 2 (LCA2) and retinitis pigmentosa (RP), specifically RP20. The most common phenotype of RPE65 mutations is severe, early-onset retinal degeneration, although some patients with RP20 may not manifest vision loss until well into their twenties. It is estimated that between 1000 and 2000 patients in the United States have biallelic *RPE65* mutations and RPE65-associated IRD.

Subretinal injection of voretigene neparvovec delivers a normal copy of the RPE65 gene to the RPE cells, which then produce the functioning RPE65 protein and restore the visual cycle. The FDA approval and evidence for efficacy of voretigene neparvovec was established with a 31-subject Phase 3 prospective clinical trial. The primary outcome measure was the ability of the subjects to navigate an obstacle course at various light levels at baseline and 1 year following voretigene neparvovec

administration. Compared to control groups, the patients who received voretigene neparvovec showed a significant improvement in their ability to complete the obstacle course at low light levels. The first patient to be treated outside the clinical trial received voretigene neparvovec in March 2018. As of August 2018, Spark announced that 12 vials of voretigene neparvovec were shipped in the second quarter of 2018, and RPE65-associated IRD patients have now been treated in 6 centers around the United States.

MeiraGTx is also developing an AAV-RPE65 gene therapy for patients with biallelic mutations in the *RPE65* gene. The MeiraGTx approach is utilizing a codon-optimized RPE65 gene that is driven by a novel synthetic RPE cell–specific promoter that is 100 to 1000 times more potent than the first-generation therapy. The Phase 1/2 clinical study has completed dosing of 9 adults in 3 escalating dose cohorts and 6 pediatric patients in the pediatric extension arm. Results from this study are forthcoming.

Choroideremia

Choroideremia, affecting approximately 1 in 50,000 males, is an X-linked recessive IRD resulting from a loss-of-function mutation in the *CHM* gene that encodes Rab escort protein 1 (REP1). Although the exact pathogenesis is poorly understood, lack of functional REP1 leads to cell death and progressive loss of choroid, RPE, and photoreceptors, ultimately resulting in blindness. Both Spark Therapeutics (SPK-7001) and Nightstar Therapeutics (NSR-REP1) are currently investigating subretinal delivery of gene therapy for *CHM*.

SPK-7001 is currently in a prospective 2-year Phase 1/2 open-label clinical trial. In a recently announced interim analysis, treatment with SPK-7001 resulted in no serious adverse events. Four of 10 later-stage subjects showed non-statistically significant indications of efficacy on 1 or more endpoints; this may be due to the late stage of the disease in this cohort. An additional cohort of 5 patients with earlier-stage disease have completed enrollment, with further safety and efficacy analysis expected to be reported by Spark in late 2018.

Nightstar recently reported that across 4 open-label Phase 1/2 clinical trials consisting of 32 subjects with choroideremia, over 90% of NSR-REP1–treated patients maintained or improved visual acuity over a 1-year period. Based on these encouraging results, Nightstar announced the initiation of a Phase 3 registration trial to study the safety and efficacy of NSR-REP1. This study is expected to enroll 140 subjects across 18 centers in the United States, Europe, Canada, and South America, with a 12-month primary endpoint of the proportion of patients with a 15-letter improvement from baseline post-treatment.

X-Linked RP

Mutations in the gene for RP GTPase regulator protein (*RPGR*) have been associated with approximately 70% of X-linked RP (XLRP). As RPGR is involved in the transport of proteins responsible for maintenance of photoreceptor health, loss of RPGR function results in progressive death of rods and ultimately cones. Males with *RPGR* mutations typically develop vision loss in the first 2 decades of life, starting with night and peripheral vision difficulties during childhood and progressing to central vision loss in their twenties and thirties. Although most female carriers are asymptomatic, some may develop vision loss similar to that seen in males.

Nightstar Therapeutics has initiated a Phase 1/2 clinical trial for the treatment of XLRP using an AAV vector with a codon-optimized RPGR gene (NSR-RPGR) that results in higher protein expression compared to that of a the wild-type RPGR coding sequence. NSR-RPGR is designed to produce the RPGR open reading frame 15 (RPGR-ORF15) protein, the configuration of RPGR expressed in the retina.

MeiraGTx is also conducting a Phase 1/2 clinical trial of AAV-RPGR in adult and pediatric patients with XLRP. In the dose-escalation phase, up to 18 adult patients will be administered 1 of 3 escalating doses. Once a suitable dose is determined in adults, the trial will expand to treat up to 12 pediatric patients with *RPGR* mutations.

In July 2018, Applied Genetic Technologies Corporation (AGTC), in collaboration with Biogen, enrolled the first patient in its own Phase 1/2 open-label, dose-escalation study of subretinal administration of an AAV-based gene therapy in patients with XLRP caused by RPGR gene mutations. Up to 15 patients will be enrolled in this ongoing study.

X-linked Retinoschisis

X-linked retinoschisis (XLRS) is characterized by an abnormal splitting of the neurosensory retina, oftentimes involving the central macula, resulting in decreased visual acuity from an early age. In addition to decreased central vision, patients with XLRS are also predisposed to increased rates of vitreous hemorrhage and retinal detachment. XLRS is caused by an abnormality in the *RS1* gene. This gene encodes a protein, retinoschisin, that is secreted by the outer retina; retinoschisin is thought to be involved in cell-cell adhesions and retinal extracellular matrix development. Deficiency in retinoschisin results in retinal cavities, retinal synaptic dysfunction, and reduced visual acuity.

The National Institutes of Health / National Eye Institute recently reported their initial findings from an intravitreal AAV8-RS1 Phase 1/2a gene therapy trial for patients with XLRS. This single-center, dose-escalating, prospective, open-label clinical trial administered intravitreal AAV8-RS1 to 9 subjects with pathogenic *RS1* mutations. AAV8-RS1 was generally well tolerated, although a dose-related ocular inflammation and dose-dependent increase in systemic AAV8 antibodies were noted in the treated patients. The schisis cavities closed transiently in 1 treated patient in the higher dose group. Additional higher doses and immunosuppressive regimens are currently being explored.

Applied Genetic Technologies Corporation (AGTC), in collaboration with Biogen, has completed enrollment in a Phase 1/2 clinical trial of rAAV2tYF-CB-hRS1 in patients with XLRS caused by mutations in the RS1 gene. Approximately 27 patients were enrolled sequentially in 4 dose-escalating groups, with the fourth group receiving the maximum tolerated dose. A group of pediatric patients was also enrolled at the middle dose range. In addition to the primary safety endpoint, visual function, retinal structure and quality-of-life measures will be evaluated following gene therapy administration. Topline data from this study are anticipated in late 2018, with the final analysis at the 12-month time point.

Achromatopsia

Congenital achromatopsia (ACHM), or rod monochromacy, is an autosomal-recessive disorder characterized by varying degrees of color blindness, nystagmus, photophobia, and severely decreased visual acuity resulting from loss of cone func-

tion. Abnormalities in 5 genes, all encoding proteins required for critical steps of the phototransduction pathway in cones, have been linked to ACHM. Mutations in the gene encoding cyclic nucleotide-gated channel beta 3 (*CNGB3/ACHM3*) are thought to be responsible for over 50% of ACHM, while mutations in CNG alpha 3 (*CNGA3/ACHM2*) are responsible for close to 25%. *CNGB3* and *CNGA3* genes encode the 2 subunits of the CNG expressed in cone outer segments. The CNGB3 and CNGA3 subunits combine to form the cone CNG channel; this channel mediates the transduction of light-triggered changes necessary for the depolarization of the cone photoreceptor cells. There are approximately 30,000 patients with ACHM in the United States.

MeiraGTx is conducting a dose-escalating Phase 1/2 open-label clinical trial of subretinally administered AAV-CNGB3 in adult and pediatric patients with *CNGB3*-associated ACHM. Up to 18 adult subjects will receive 1 of 3 doses of AAV-CNGB3. Once an acceptable dose is established in adults, up to 9 pediatric patients will be treated.

AGTC is currently conducting 2 separate Phase 1/2 clinical trials to evaluate the safety and efficacy of AAV gene therapy for the 2 most common forms of ACHM, those caused by a mutation in either *CNGB3* or *CNGA3*. As with the MeiraGTx study, the AGTC studies are currently enrolling.

Other IRDs

In addition to the above-mentioned IRDs, upwards of a dozen gene therapy treatments for a variety of disorders are in late preclinical or early Phase 1 stage. These include treatments for Leber congenital amaurosis due to abnormalities in the centrosomal protein of 290 kDa (*CEP290* gene), Stargardt disease secondary to ATP-binding cassette, sub-family A, member 4 (*ABCA4 gene)* protein, and Best disease due to mutations in the Bestrophin-1 protein (*BEST1 gene)*, among others.

Gene Therapy for Acquired Retinal Disorders

Although the exciting developments outlined above have shown the proof-of-concept for ocular gene therapy as a viable therapeutic option for the treatment of single-gene IRDs, application of gene therapy techniques to more multifactorial and oftentimes noninherited disorders (eg, AMD, diabetic retinopathy, etc.) would represent a true paradigm shift for millions of patients. The overarching concept for gene therapy here is to introduce a transgene that is not otherwise found in the target cell (eg, an anti-VEGF molecule for the treatment of exudative, or wet, AMD (wAMD), rather than to fix a specific inherited genetic abnormality. The eye can then become a "biofactory" that produces the transgene indefinitely, obviating the need for repeated intravitreal anti-VEGF injections, for example, in the case of wAMD.

Dry AMD

Several lines of evidence have strongly implicated a role for the complement pathway in the pathogenesis and progression of AMD. Polymorphisms in complement activators and complement inhibitors have been associated with progression to advanced AMD. The terminal step in the complement pathway involves the activation of the membrane attack complex (MAC), which ultimately results in lysis and death of the target cell. CD59, also known as MAC-inhibitory protein (MAC-IP) or membrane inhibitor of reactive lysis (MIRL) or protectin, can prevent C9 from polymerizing and forming the MAC. Preclinical studies indicate that the soluble form of CD59 (sCD59) delivered via an intravitreal gene therapy approach may be a potential therapy for both the wet and dry forms of AMD.

Hemera Biosciences is currently conducting a single-center, Phase 1, open-label, dose-escalating, safety and tolerability study of a single intravitreal administration of AAV-based sCD59 gene therapy (AAVCAGsCD59, HMR59) in patients with advanced dry AMD with geographic atrophy. Approximately 17 patients are expected to be enrolled, with an initial study readout at 26 weeks and with subjects followed for an additional 18-month safety evaluation.

Exudative AMD

Over the past decade, the advent of anti-VEGF therapy has revolutionized our approach to the treatment of exudative AMD (wAMD). With repeated intravitreal administrations, patients with wAMD can expect to maintain or even gain vision. What was once a blinding disease has now become a chronic disorder that requires near-monthly injections for the lifetime of a patient. A gene therapy approach could potentially obviate the need for repeated intraocular injections by delivering an anti-VEFG transgene via a single procedure and turning cells of the eye into anti-VEGF producing biofactories.

Several completed dose-escalating Phase 1/2 gene therapy trials have failed to show sufficient efficacy to move beyond the initial clinical experience. The most notable among these disappointments include the intravitreal AAV2-sFLT01 from Genzyme and the subretinal rAAV.sFlt-1 from Avalanche, both tested in non–treatment naïve patients with wAMD. These discouraging outcomes may stem from an assortment of causes, including the choice of gene therapy vector (AAV and AAV2), the specific route of administration (intravitreal and subretinal), and/or the selection of transgene (both had variations on the naturally occurring soluble fms-like tyrosine kinase-1, known as sFlt-1 or sVEGFR-1). More recent approaches for gene therapy for wAMD have tried to learn from these previous clinical trials.

RegenXBio recently announced that the first 18 subjects had been enrolled in a Phase 1, open-label, multiple-cohort, dose-escalation study to evaluate the safety and tolerability of gene therapy with RGX-314 in non–treatment naïve patients with wAMD. RGX-314 uses a proprietary AAV8 vector that contains a transgene for a monoclonal antibody fragment (similar to ranibizumab) that binds to and neutralizes VEGF. RGX-314 is administered via a subretinal injection following a pars plana vitrectomy. RegenXBio reported that RGX-314 was well tolerated and showed signs of dose-dependent biological activity (as measured by protein levels, OCT, and need for rescue injections). Enrollment of a fourth cohort of wAMD subjects receiving a higher dose of RGX-314 is currently under way. Based on the data from the first 3 cohorts, RegenXBio plans to initiate a Phase 2 multicenter clinical trial with RGX-314 in 2019.

In late July 2018, Adverum submitted an Investigational New Drug (IND) application to the FDA to evaluate ADVM-022 (AAV7m8-aflibercept) in patients with wAMD. ADVM-022 uses a proprietary vector developed via directed evolution (AAV7m8) to allow for robust retinal cell transfection following an intravitreal injection (a feat typically not possible with traditional AAV or AAV2 vectors). The transgene carried by ADVM-022 is an anti-VEGF molecule similar to aflibercept. In preclinical non-human primate models, ADVM-022

induced sustained intraocular expression of aflibercept for up to 16 months following a single intravitreal injection. After 13 months, a single intravitreal injection of ADVM-022 was found to be safe and statistically significant in preventing the development of laser-induced choroidal neovascular lesions when compared to the vehicle control group. A Phase 1/2 clinical trial is upcoming.

AGTC has also announced that they have a preclinical program focusing on AMD, although specific details, including transgene and target patient population (dry or wet AMD), are yet to be revealed.

Conclusion

With the groundbreaking FDA approval of Luxturna from Spark Therapeutics, 2018 will mark the year in which gene therapy entered our therapeutic armamentarium. As targeted gene therapy treatment options for IRDs continue to expand (mostly in the form of an ever-growing number of clinical trials), genetic testing for more precise molecular diagnosis of patients with retinal degenerations will become increasingly important. While the proof of concept was gained from our experience with rare IRDs, gene therapy has the potential to transform our approach to much more prevalent conditions, such wAMD. Continued success for ocular gene therapy will undoubtedly depend on capsid selection (AAV8, AAV9, AAV7m8, etc.), gene cassette optimization (including choice of transgene, promotors, and enhancers), formulation, manufacturing, and appropriate route of delivery (intravitreal vs. subretinal).

An Injectable Fluocinolone Implant for Posterior Uveitis: One-Year Results From Two Phase 3 Clinical Trials

Glenn J Jaffe MD

Noninfectious uveitis that affects the posterior segment (including intermediate, posterior, and panuveitis) is a group of diseases that typically run a chronic course and for which long-term therapy is needed. Intraocular sustained drug delivery has been shown to be a rational approach to effect this type of long-term treatment. The current FDA-approved long-term intraocular sustained drug delivery insert, a fluocinolone acetonide intraocular delivery system, must be implanted surgically in the operating room.[1-3] Ideally, it would be possible to place a long-term delivery system in the clinic, in an injectable format, to minimize expense and the risks associated with surgical placement. To meet this need, an injectable fluocinolone acetonide insert (FAi) delivering daily intravitreal microdoses has been developed to treat chronic noninfectious uveitis that affects the posterior segment. Jaffe and coworkers described a favorable treatment effect with this implant in a randomized, individual investigator–initiated trial.[4]

To further evaluate the usefulness of this approach, 2 multicenter, randomized, masked, 3-year safety and efficacy studies of an injectable FAi are being conducted. Both studies include subjects with a history of recurrent noninfectious uveitis of less than 1 year duration affecting the posterior segment of the eye. Study 1, conducted in the United States, Europe, the Middle East, and India, included mostly white women age 40 to 60 with a disease duration of 7.8 ± 6.7 years. Study 2, conducted in India, included mostly Asian females age 20 to 40 with a disease duration of 3.1 ± 3.0 years. A total of 282 subjects were enrolled and randomized to treatment with a single FAi (188) or sham injection (94) in the eye with more severe disease. Safety and efficacy, including the primary endpoint, the 6-month, and also the 1-year recurrence rates, were evaluated.

The 6-month and 1-year uveitis recurrence rates were significantly reduced in the FAi- vs. sham-injected eyes in both studies. At 6 months, the recurrence rates in the FAi-treated and sham-treated subjects, respectively, were 28% vs. 91% in Study 1 and 26% vs. 60% in Study 2 ($P < .001$). Differences remained significant at 12 months. Resolution of baseline macular edema was more frequently reported in FAi-injected eyes. VA was stable or improved in >75% of all study eyes in both studies. IOP >30 mmHg was seen in 13% and 15% of FAi eyes vs. 5% and 2% of sham eyes in Studies 1 and 2, respectively. Cataract surgery in FAi eyes was more common in Study 1 (33%) than in Study 2 (18%); the rates in sham-injected eyes (5% and 9%, respectively) were lower. Data from these studies have been submitted to the FDA to gain approval to use this injectable implant to treat patients with uveitis that affects the posterior segment.

Overall, the intravitreal FAi injection very effectively reduced noninfectious posterior segment uveitis recurrences in a diverse group of subjects. No unanticipated safety findings were noted. Extended, continuous control of inflammation using an in-office injection appears achievable with the FAi.

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TIE2 Activation for Treatment of Diabetic Retinopathy and Diabetic Macular Edema

Peter K Kaiser MD

I. Rationale

A. Tie2 pathway and vascular health

1. Tie2 is a transmembrane receptor expressed on vascular endothelial cells.
2. Tie2 is activated in healthy vessels, serving as the "gatekeeper" of vascular quiescence.[1-3]
   a. Maintains integrity of endothelial cell junctions
   b. Enhances endothelial cell function and viability
   c. Inhibits vascular inflammation
3. Tie2 has two ligands: angiopoietin 1 (Ang-1,) which activates Tie2, and angiopoietin 2 (Ang-2), which serves as a context-dependent antagonist (weak agonist).
4. Tie2 is also deactivated by the endothelial transmembrane protein VE-PTP (vascular endothelial protein tyrosine phosphatase).

B. Tie2 pathway dysfunction and diabetic retinopathy (DR)

1. Ischemic retinopathies including DR and retinal vein occlusion (RVO) are associated with upregulated Ang-2 and VE-PTP, which leads to Tie2 inactivation and vascular dysfunction and destabilization.
2. Hyperglycemia-induced Tie2 inactivation likely plays a role in pericyte dropout and capillary loss in the initial stages of diabetic retinopathy.[4,5]
3. Tie2 inactivation is also responsible for vascular dysfunction in other diabetic vasculature beds (eg, kidney).

C. Pharmacologic approaches for Tie2 restoration in DR

1. Ang-2 inhibition: blocks competitive binding of Ang-2 to the Tie2 receptor, allowing activation via Ang-1
2. VE-PTP inhibition: activates Tie2 independent of Ang-1 or Ang-2 levels

II. Programs in Development

A. Intravitreal injection-based Ang2 inhibitor programs for treatment of diabetic macular edema (DME) and exudative AMD

1. RG7716 (Roche / Genentech)
   a. Anti-Ang2, anti-VEGF bispecific antibody
   b. BOULEVARD: Positive Phase 2 DME study demonstrated clinically and statistically significant BCVA improvement compared to 0.3-mg ranibizumab, as well as higher percentage of patients with more than 2-step improvement in Diabetic Retinopathy Severity Scale (DRSS).
   c. Pivotal Phase 3 targeted to start early 2019
2. Nesvacumab / aflibercept (Regeneron / Bayer)
   a. Coformulated Anti-Ang-2 fully human mAb Nesvacumab (REGN-910) + aflibercept
   b. RUBY: Phase 2 DME study showed signal of beneficial effect for Tie2 /VEGF inhibition compared to aflibercept alone (center subfield reduction and improved DRSS).
   c. Program is currently on hold due to tougher regulatory hurdle for combination product (requires statistically significant improvement over monotherapy).

B. Non–intravitreal-based program for treatment of DR

1. AKB-9778 (Aerpio)
   a. Small molecule inhibitor of VE-PTP
   b. Subcutaneous administration
      i. Allows for treatment of both eyes (DR bilateral in majority of patients)
      ii. Potential for benefits of Tie2-restoration in other diabetic vascular beds where complications are also linked to Tie2 dysfunction (eg, kidney)

c. TIME-2: Completed Phase 2a study[6]
   i. Randomized, parallel-group, double-masked, 3-month treatment study in patients with DME in study eye
   ii. AKB-9778 + ranibizumab monthly IVT demonstrated greater reduction in DME than ranibizumab monthly monotherapy (–164 µm vs. –110 µm, $P = .008$).
   iii. This study also provided evidence that AKB-9778 monotherapy may be effective in decreasing the severity of diabetic retinopathy in both eyes.

d. TIME-2b: Ongoing Phase 2b study
   i. Randomized, placebo-controlled, double-masked, 48-week treatment study in patients with moderate to severe NPDR *without* DME; primary outcome is improvement in DRSS.
   ii. Recruitment completed in February 2018. Top-line results anticipated early Q2 2019.

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Combined Blockade of Angiopoeitin-2 and VEFG-A With RG7716 in Phase 2 Diabetic Macular Edema and Neovascular AMD Trials: What's New and What's to Come

Charles C Wykoff MD PhD

Background

Diseases of the retina associated with abnormal vascular growth and leakage, including diabetic macular edema (DME) and neovascular AMD (nAMD), are leading causes of vision loss around the world.[1] For over a decade, the standard of care for the treatment of most exudative retinal disorders has been neutralization of vascular endothelial growth factor-A (VEGF), and intravitreal anti-VEGF therapies have greatly improved visual and anatomic outcomes for many patients.[2] However, due to both efficacy and durability limitations of current generation anti-VEGF monotherapies, there is a pressing need for therapies that target complimentary pathways to facilitate improved outcomes and reduced treatment burden for patients with exudative retinal diseases.

DME and nAMD are multifactorial diseases involving multiple pathways that are not completely addressed with anti-VEGF monotherapy. Angiopoietin-1 and -2 (Ang-1 and Ang-2) belong to a family of vascular growth factors and play key roles in vascular development and homeostasis.[3] The VEGF and Ang-2 pathways interplay, and when pathologically overexpressed this can lead to inflammation, pericyte loss, and endothelial cell destabilization, resulting in breakdown of the blood–retinal barrier with accompanying vascular leakage and ultimately neovascularization.[3] In vivo models of diabetic retinopathy have demonstrated that Ang-2 and VEGF work synergistically to induce vessel destabilization and neovascularization.[4] Elevated levels of Ang-2 have been detected in the vitreous of diabetic and nAMD patients,[5] and colocalized expression of VEGF and Ang-2 has also been demonstrated within surgically excised choroidal neovascularization (CNV) lesions from nAMD patients.[6] Dual inhibition of VEGF and Ang-2 could potentially improve the management of retinal vascular diseases compared to anti-VEGF monotherapy.

Development of and Clinical Application of RG7716

Preclinical and Phase 1 Study

RG7716 is the first bispecific antibody designed specifically for intravitreal use.[5,7,8] This novel antibody, generated using CrossMAb technology,[5] simultaneously binds and neutralizes VEGF and Ang-2 with high specificity and potency. The Fc region of RG7716 is engineered with 6 point mutations to abolish binding to the neonatal Fc-receptor and the Fc-gamma receptor to reduce systemic exposure and proinflammatory potential. A Phase 1 single and multiple ascending-dose study assessed safety of RG7716 in 24 nAMD patients refractory to anti-VEGF monotherapy.[7] RG7716 was well tolerated up to the highest 6 mg dose with no safety concerns identified. Median BCVA gains of +7 letters from baseline at 28 days were reported after the last intravitreal dose administration in the combined single-dose and 6-mg multiple-dose cohorts.

Phase 2 Studies

Three prospective, randomized Phase 2 trials assessed the safety, efficacy, and durability of RG7716: BOULEVARD (clinicaltrials.gov NCT02699450) for DME and AVENUE (NCT02484690) and STAIRWAY (NCT03038880) for nAMD.

Methods of Phase 2 Trials

Details for the three Phase 2 prospective, randomized, active-comparator controlled, double-masked, multicenter studies, which evaluated the safety, efficacy, and durability of intravitreal RG7716 compared with anti-VEGF monotherapy, are presented in Figures 1-3.

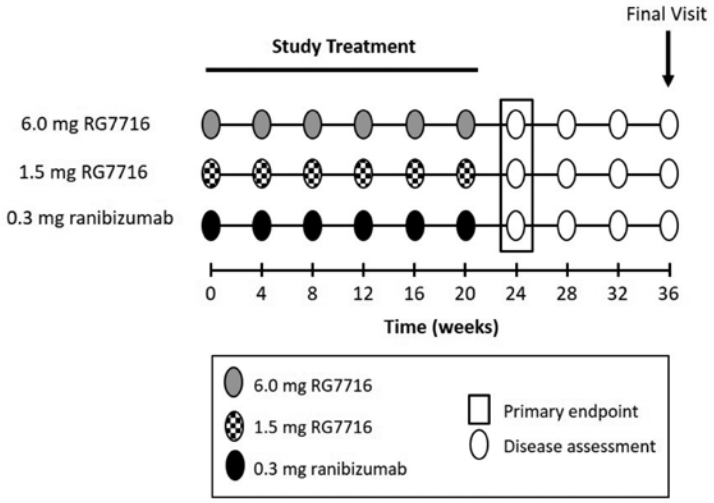

Figure 1. Study design for BOULEVARD trial.

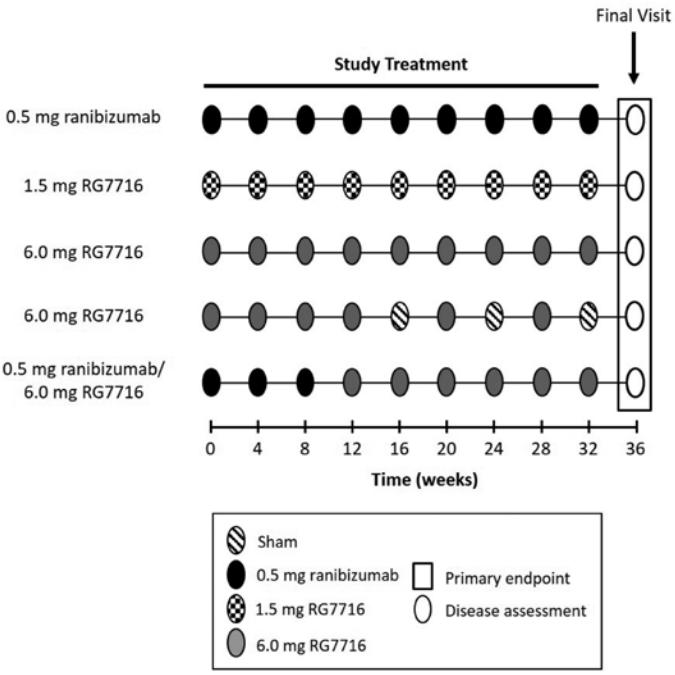

Figure 2. Study design for AVENUE trial.

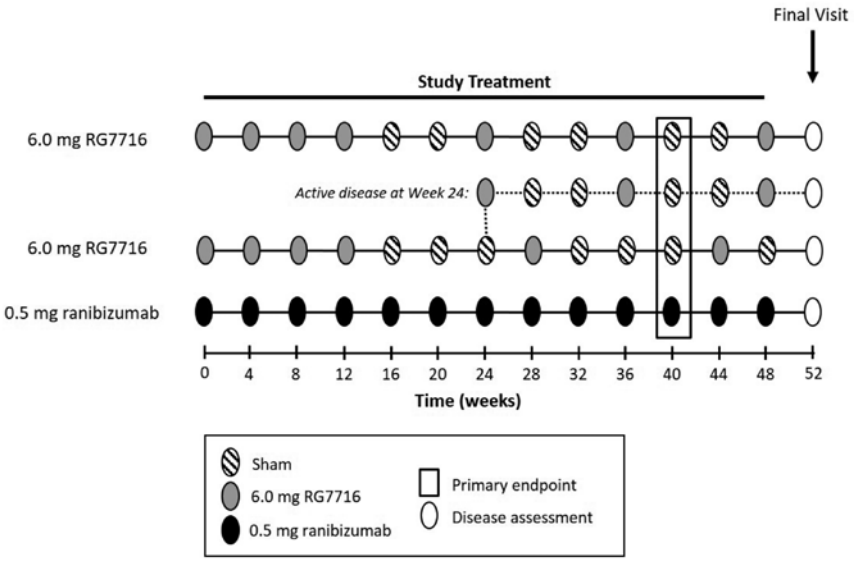

Figure 3. Study design for STAIRWAY trial.

Results of BOULEVARD Phase 2 Trial

- In BOULEVARD, RG7716 met its primary endpoint, resulting in clinically meaningful and statistically significant improvements in visual acuity from baseline in patients with DME.
- Patients treated with 6.0-mg RG7716 achieved a +13.9 mean BCVA letter gain over baseline at Week 24, with a statistically significant +3.6-letter gain over 0.3-mg ranibizumab ($P = 0.03$; 80% CI, 1.53-5.61).
- There was a 32% relative increase in the proportion of patients achieving ≥15 BCVA letter gains from baseline at Week 24 with 6.0-mg RG7716 relative to 0.3-mg ranibizumab.
- Numerically greater reductions in central subfield thickness were observed with RG7716 over anti-VEGF monotherapy (adjusted mean changes: –204.7 vs. –225.8 microns with 0.3-mg ranibizumab or 6.0-mg RG7716, respectively).
- More patients treated with RG7716 experienced a ≥2-step improvement in DRSS (12%, 28%, and 39% with 0.3-mg ranibizumab, 1.5-mg RG7716, or 6.0-mg RG7716, respectively).
- RG7716 treatment also demonstrated the potential for extended durability compared to 0.3-mg ranibizumab, with a higher proportion of patients treated with RG7716 maintaining disease stability than those receiving ranibizumab during the off-treatment observation period.
- RG7716 was well tolerated, with a safety profile comparable to that of anti-VEGF monotherapy.

Discussion and Future Outlook for RG7716 in the Management of Exudative Retinal Diseases

- Cumulatively, preclinical, Phase 1, and Phase 2 data all support the rationale for targeting the Ang-2 pathway in an attempt to improve outcomes among patients with exudative retinal diseases beyond anti-VEGF monotherapy.
- Data from the BOULEVARD Phase 2 trial show that for patients with center-involving DME, dual inhibition of VEGF and Ang-2 has the potential to improve visual and anatomic outcomes with improved durability of effect compared to anti-VEGF monotherapy.
- A global Phase 3 trial program will be initiated to confirm the efficacy, safety, and durability profile of RG7716 in patients with DME.

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The Art and Science of YAG Vitreolysis

Chirag P Shah MD MPH

Patients are often more bothered by their floaters than they are of potentially blinding disease, like AMD or diabetic retinopathy. Only 3 treatment options exist: observation and reassurance (which I employ 99.9% of the time), YAG vitreolysis, and vitrectomy.

Vitrectomy is the most definitive way to remove floaters, but it does carry a small risk of serious complication, such as endophthalmitis or retinal detachment, not to mention the guaranteed risk of cataract formation in phakic patients. YAG vitreolysis may serve as an intermediary treatment option, with potentially less risk but less reward compared to vitrectomy. Unsuccessful YAG vitreolysis could be followed by vitrectomy, if desired.

YAG vitreolysis has a bad reputation in the retina community for a variety of justified reasons. There are limited safety and efficacy data. The procedure is highly commercialized by laser-for-floaters doctors. The procedure is not FDA approved, and there is no dedicated billing code (though some providers use "severing vitreous strands," 67031). In the setting of the aforementioned limitations, the out-of-pocket cost for YAG vitreolysis is typically $1,000-$2,000 per eye.

However, we may be in the midst of a long, slow paradigm shift. Emerging data suggest that there may be merit to studying YAG vitreolysis further. My group conducted the first randomized controlled trial comparing YAG vitreolysis to sham laser for symptomatic Weiss ring floaters.[1] This pilot study of 52 eyes (36 in the YAG arm, 16 in the control arm) found that 53% of patients treated with 1 YAG vitreolysis session reported significant or complete resolution of their floaters symptoms, compared to no patients in the control arm (difference, 53%; 95% CI, 36%-69%, $P < .001$). There were no differences in adverse events by the end of the 6-month study. We are currently conducting an extension study to determine if these efficacy results are sustained 2-3 years after treatment, to document any long-term adverse events, and to determine if there is additional benefit to a second YAG vitreolysis session in those unsatisfied. Further, there is an ongoing multicentered randomized controlled trial in Japan.

Singh presented a poster at AAO 2017 detailing adverse events in a retrospective case series of 1272 eyes.[2] To my knowledge, this is the largest known case series of eyes treated with YAG vitreolysis. He reported low rates of complications, including 7 IOP spikes (0.6%, required topical drops), 2 crystalline lens damage (0.2%, 1 required cataract surgery and recovered 20/20 vision, the other was observed), and 1 retinal hemorrhage (0.1%, resolved in 3 months, no sequelae). There were no retinal detachments.

The American Society of Retina Specialists Research and Safety in Therapeutics (ASRS ReST) Committee reported similar adverse events after YAG vitreolysis, with the addition of retinal tears, retinal detachments, scotomas, and an increased number of floaters.[3] There was no denominator, so we cannot calculate rates with this surveillance report.

Given the encouraging results of our pilot study and a reasonable safety profile thus far, the next step in the development of YAG vitreolysis would be a large, U.S.-based, randomized, multicentered clinical trial. Such a trial would include many floater types and allow for multiple treatment sessions, if needed. Ideally, this trial would be an FDA-registration trial, earning FDA approval if the results were positive, as well as a proper billing code. Presently, there is no funding for such a trial.

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Apl-2 Treatment for Geographic Atrophy: Long-term Results

David S Boyer MD

Introduction

Geographic atrophy (GA) is an advanced form of AMD characterized by progressive and irreversible loss of the retinal pigment epithelium, photoreceptors, and underlying choriocapillaris. These lesions typically appear first in the perifoveal macular; however, with time these lesions expand, resulting in visual function loss including reading, driving, and recognizing faces. GA is estimated to affect approximately 5 million people globally, and its prevalence increases exponentially with age. Currently, there are no approved treatments to reverse or reduce the GA progression.

Methods

The FILLY Phase 2 trial was a multicenter, randomized, 18-month, single-blind, sham-controlled study to evaluate the safety, tolerability, and efficacy of APL-2, a complement C3 inhibitor, in patients with GA secondary to AMD. 246 subjects were enrolled to receive intravitreal injection of APL-2 monthly, APL-2 every other month, or sham for 12 months, followed by 6 months of safety monitoring without treatment. The primary endpoint was the mean change in square root GA lesion measured by fundus autofluorescence from baseline to Month 12. Secondary outcome measures included safety and visual acuity.

Results

The primary endpoint was met. Monthly administration of APL-2 showed a 29% (95% CI, $P = .008$) reduction in the GA lesion growth compared to sham at Month 12. With the every-other-month administration, a 20% reduction (95%; $P = .067$) was observed at Month 12. A more pronounced effect was observed during the second 6 months of treatment, with observed reductions of 45% (95% CI; $P < .001$) and 33% (95% CI; $P = .009$) for APL-2 monthly and every other month, respectively. During the 6 off-treatment months, the growth rate between groups was similar. No difference in visual acuity was observed between the groups. New-onset exudation was reported more frequently in APL-2 treated eyes. The safety profile was consistent with other IVT injection therapy.

Conclusion

The inhibition of complement C3 by APL-2 demonstrated statistically significant reductions in GA growth as compared to sham groups, with an acceptable safety profile. The risk / benefit profile supports the start of the Phase 3 study.

A Simple OCT-Based System for Staging Dry AMD

Srinivas R Sadda MD

I. Background

A. Color photography has been the historical gold standard for staging intermediate AMD and assessing risk of progression.

B. Identifying drusen area, large drusen, and pigment abnormalities appears to be most important for accurate staging.

C. Grading systems have been developed based on color photos.

1. Prime example: International ARM Epidemiological Study Group Scale[1]

a. Grading schemes confined by the limitations of analog / film photography

b. Appearance and severity of dry AMD lesions graded using standard grid and sizing circles. Lesions graded:

i. Drusen

ii. Pigmentary abnormalities (hypo and hyper pigmentation)

iii. Geographic atrophy

2. Age-Related Eye Disease Study (AREDS) investigators were able to use the grading system to develop a severity scale for AMD that predicted risk of progression to advanced AMD.

a. The 9-step AREDS scale was quite effective for predicting progression risk, but too cumbersome for use in practice.[2]

b. The 4-point AREDS simple scale based on identifying large drusen and pigment changes in each eye was more clinically practical and suitable for use in practice, but perhaps not granular enough for research applications.[3]

II. Rationale

A. OCT has largely replaced color photography as our key imaging modality in clinical practice.

B. Features of intermediate AMD (eg, drusen, pigment migration) are clearly seen on OCT.

C. Many OCT risk factors for progression to advanced AMD have been defined.

1. Hyporeflective foci within drusen

2. Hyperreflective foci in the retina

3. Subretinal drusenoid deposits

4. High central drusen volume (> 0.03 mm^3 within the central 3 mm)

D. Key study question: Can these known OCT risk factors be blended together to create an OCT-derived severity scale based on the risk for progression to late AMD?

III. Study Methods

A. Retrospective study

B. Consecutive patients with intermediate AMD in at least 1 eye at baseline

C. Minimum 6 months follow-up

D. Cirrus OCT (for drusen volume) at baseline (512 x 128 macular cube)

E. If both eyes eligible, only right eye included for study

F. Baseline OCT evaluated for:

1. Hyporeflective foci within drusen

2. Intraretinal hyperreflective foci

3. Subretinal drusenoid deposits

4. Drusen volume ≥ 0.03 mm^3 within 3-mm circle (automatic)

G. Follow up OCTs (and other clinical data) evaluated for progression to atrophy or CNV

H. Baseline OCT factors correlated with progression to advanced AMD (Spearman)

IV. Results

A. Total cohort = 163 patients

B. Intermediate AMD O.U.: $n = 28$

C. Fellow eye with at least some advanced AMD: $n = 131$

D. Fellow eye < intermediate AMD: $n = 4$

E. Mean age: 80.3 ± 7.9 (63-96)

F. Mean follow-up (months): 25.5 ± 14.6 (6-64)

G. Risk factors for progression to advanced AMD (total cohort): see Table 1

H. Risk factors for progression to advanced AMD (subset 24 months or more follow-up): see Table 2

I. Construction of simple scale (point-rating system)

1. Intermediate AMD O.U. (maximum of 8 points): see Table 3

2. Fellow eye with advanced AMD (minimum of 4 points): see Table 4

J. Predicting progression to advanced AMD at final follow-up (mean 2 years): see Table 5

Table 1.

Progression to Advanced	Drusen Volume ≥ 0.03 mm^3	IHRF	Hyporeflective Drusen	SDD
Advanced AMD (GA and/or CNV)	$r = 0.228$	$r = 0.506$	$r = 0.427$	$r = 0.304$
	$P = 0.003$	$P < 0.001$	$P < 0.001$	$P < 0.001$
GA only	$r = 0.236$	$r = 0.448$	$r = 0.361$	$r = 0.284$
	$P = 0.002$	$P < 0.001$	$P < 0.001$	$P < 0.001$
CNV only	$r = -0.002$	$r = 0.254$	$r = 0.188$	$r = 0.186$
	$P = 0.979$	$P = 0.001$	$P = 0.016$	$P = 0.018$

Abbreviations: GA, geographic atrophy; IHRF, intraretinal hyperreflective foci; SDD, subretinal drusenoid deposits.

Table 2.

Progression to Advanced	Drusen Volume ≥ 0.03 mm^3	IHRF	Hyporeflective Drusen	SDD
Advanced AMD (GA and/or CNV)	$r = 0.253$	$r = 0.548$	$r = 0.406$	$r = 0.303$
	$P = 0.030$	$P < 0.001$	$P < 0.001$	$P = 0.009$
GA only	$r = 0.255$	$r = 0.513$	$r = 0.379$	$r = 0.317$
	$P = 0.028$	$P < 0.001$	$P < 0.001$	$P = 0.006$
CNV only	$r = 0.024$	$r = 0.225$	$r = 0.119$	$r = 0.150$
	$P = 0.836$	$P = 0.054$	$P = 0.312$	$P = 0.201$

Abbreviations: GA, geographic atrophy; IHRF, intraretinal hyperreflective foci; SDD, subretinal drusenoid deposits.

Table 3.

Risk Factors	Scores O.D.	Scores O.S.
Hyporeflective drusen	Yes: 1	Yes: 1
	No: 0	No: 0
Intraretinal HRF	Yes: 1	Yes: 1
	No: 0	No: 0
SDD	Yes: 1	Yes: 1
	No: 0	No: 0
Drusen volume > 0.03 mm^3	Yes: 1	Yes: 1
	No: 0	No: 0

Abbreviations: HRF, hyperreflective foci; SDD, subretinal drusenoid deposits.

Table 4.

Risk Factors	Scores (Intermediate AMD)	Scores (Fellow Eye)
Hyporeflective drusen	Yes: 1	4
	No: 0	
Intraretinal HRF	Yes: 1	4
	No: 0	
SDD	Yes: 1	4
	No: 0	
Drusen volume > 0.03 mm^3	Yes: 1	4
	No: 0	

Abbreviations: HRF, hyperreflective foci; SDD, subretinal drusenoid deposits.

Table 5.

Risk Categories	I	II	III	IV
Cumulative score	0, 1, 2	3, 4	5, 6	7, 8
Progression rate	0% (0/15)	11% (5/45)	42% (29/69)	71% (24/34)

V. Summary/Conclusion

A. Several OCT features appear to increase the risk for late AMD.

1. Drusen volume ≥ 0.03 mm^3 (within the central 3 mm), intraretinal hyperreflective foci, hyporeflective drusen, subretinal drusenoid deposits
2. Intraretinal hyperreflective foci appeared to be the strongest individual predictor.

B. These factors may be merged into a scoring system that appears to predict risk for late AMD.[4]

C. If replicated in future larger prospective studies, this simple OCT-based system may be useful for clinical trials and practice.

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The Natural History of Geographic Atrophy in AREDS2

Emily Y Chew MD and the AREDS2 Investigators

Purpose and Background

The aim of this presentation is to present the prevalence, incidence, and clinical characteristics of eyes with geographic atrophy (GA) associated with AMD, including the clinical and genetic factors that affect the enlargement of GA.

GA in AMD is thought to affect over 8 million people worldwide.[1] It represents an important clinical and research priority, as no treatments are routinely available in clinical practice to treat GA, prevent its occurrence, or decrease its enlargement rate. However, several potential strategies to slow down the enlargement rate of GA are currently under investigation, including those based on inhibition of the complement system.[2-4] In these and previous clinical trials, change in GA area over time has been used as the primary outcome measure, with approval of this measure by the FDA as a clinically important endpoint.[5-9] For these reasons, natural history data regarding the development and progression of GA may be useful. In addition, information on clinical and genetic factors that influence GA enlargement may provide insights into pathogenesis and may aid recruitment and stratification of patients into clinical trials.

Method

This is a prospective, longitudinal study within a cohort followed for a randomized clinical trial of lutein / zeaxanthin and omega-3 fatty acids for the treatment of AMD, the Age-Related Eye Disease Study 2 (AREDS2). Participants aged 50 to 85 years were enrolled and followed on the average for 5 years. Baseline and annual stereoscopic color fundus photographs were evaluated for GA presence and area. Analyses included GA prevalence and incidence rates, Kaplan-Meier rates, mixed-model regression and multivariable analysis of square root of GA area adjusted for covariates, including clinical / imaging characteristics and genotype. The main outcome measures were presence or development of GA and the change in square root of GA area over time.

Results

At baseline, 517 eyes (6.2%) of 411 participants (9.8%) had pre-existing GA (without neovascular AMD), with the following characteristics: 33% central, 67% noncentral and configuration (36% small, 26% solid / unifocal, 24% multifocal, 9% horseshoe / ring, and 6% indeterminate). Of the remaining 6530 eyes at risk, 1099 eyes (17.3%) of 883 participants developed incident GA without prior neovascular disease during mean follow-up of 4.4 years. The Kaplan-Meier rate of incident GA was 19% of eyes at 5 years. In eyes with incident GA, 4-year risk of subsequent neovascular AMD was 29%. In eyes with incident noncentral GA, 4-year risk of central involvement was 57%. GA enlargement rate (following square root transformation) was similar in eyes with pre-existing GA (0.29 mm/year; 95% CI, 0.27-0.30) and incident GA (0.28 mm/year; 95% CI, 0.27-0.30). In the combined group, GA enlargement was significantly faster with noncentrality, multifocality, intermediate baseline size, and bilateral GA ($P < .0001$ for interaction in each case) but not with AREDS2 treatment assignment ($P = .33$) or smoking status ($P = .05$).

Genetics Results

Enlargement was significantly faster with *ARMS2* risk ($P < .0001$), *C3* nonrisk ($P = .0002$), and *APOE* nonrisk ($P = .001$) genotypes.

Conclusions

Analyses of AREDS2 data on natural history of GA provide representative data on GA evolution and enlargement. GA enlargement, which was influenced by lesion features, was relentless, resulting in rapid central vision loss. The genetic variants associated with faster enlargement were partially distinct from those associated with risk of incident GA. These findings are relevant to further investigations of GA pathogenesis and clinical trial planning.

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Does the OCT Double Layer Sign in Nonexudative Macular Diseases Indicate Subclinical Neovascularization?

Philip J Rosenfeld MD PhD and Yingying Shi MD

Introduction

On OCT imaging, Sato et al were the first to describe the double layer sign (DLS), which was observed on B-scans from eyes with polypoidal choroidal vasculopathy (PCV).[1] The DLS consisted of 2 highly reflective layers that represented a separation between the retinal pigment epithelium (RPE) and the Bruch membrane (BM). This DLS was actually a low-lying, irregular retinal pigment epithelial detachment (PED) that corresponded to the region containing the branching vascular network (BVN) identified by indocyanine green angiography (ICGA). This DLS also appears to be a common feature associated with the more typical type 1 macular neovascularization (MNV) in AMD, and now, BVNs are considered to be a variant of type 1 MNV. As a result, Dansingani et al have proposed that PCV should be renamed "aneurysmal type 1 MNV."[2]

While structural OCT imaging identifies the DLS, ICGA and OCT angiography (OCT-A) can visualize the nonexudative type 1 MNV associated with the DLS.[3-14] It's important to identify these subclinical neovascular lesions since they have a higher annual risk of exudation compared with AMD eyes that don't have these lesions.[4] ICGA can be used to detect subclinical MNV, but it's not practical to use ICGA as a screening tool due to its cost, invasiveness, risks, inconvenience, and discomfort.

OCT-A is noninvasive, safer, less expensive to perform, more convenient, and more comfortable for the patient than ICGA. However, the OCT-A instruments are not yet widely available. They are more expensive to purchase than traditional OCT, and the procedure is not yet reimbursed by Medicare or private insurance even though it takes more time to interpret the images and more storage capacity is needed for the image files. Currently in the United States, OCT-A is reimbursed at the same level as traditional OCT imaging. However, when an OCT-A scan is performed, both structural and flow images are generated, so it provides the value of a traditional OCT structural scan with the advantages of an OCT angiographic flow scan.

While obtaining OCT-A scans on type 1 MNV or BVNs, we were able to observe that in nonexudative AMD eyes the presence of a DLS was associated with the presence of type 1 MNV. Since structural OCT instruments are widely available, we wanted to determine if the DLS on structural OCT images could be used in lieu of OCT-A imaging to reliably detect subclinical type 1 MNV. To test the predictive value of the DLS seen on structural OCT B-scans with swept source OCT-A (SS-OCT-A) imaging of eyes with and without subclinical MNV, we performed a masked grading of eyes with intermediate or late nonexudative AMD.

Masked Grading of AMD Eyes With and Without Subclinical MNV

AMD eyes with intermediate and late nonexudative AMD were enrolled in a prospective SS-OCT-A imaging study at the Bascom Palmer Eye Institute. A total of 100 eyes were chosen based on the presence or absence of subclinical, nonexudative MNV based on SS-OCT-A scans. Three graders with experience in interpreting OCT-A images of MNV were enlisted to perform a masked grading of these 100 eyes for the presence or absence of a DLS based on OCT B-scans. The graders only had access to the structural B-scans and the total en face structural images from these eyes. For all graders, there were statistically significant associations between the DLS and subclinical MNV ($P <$ .001). The sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) for the graders were calculated and compared. Overall, the sensitivity outcomes ranged from 73% to 83%, specificity ranged from 84% to 87%, PPV ranged from 69% to 76%, and NPV ranged from 86% to 94%.

Can Structural OCT Replace OCT-A for the Detection of Subclinical MNV?

While the DLS showed a statistically significant association with the presence of type 1 MNV, there were instances where the graders failed to detect the MNV. Most commonly, the graders missed neovascular lesions that were small with RPE elevations that were interpreted to resemble typical drusen. Moreover, in a few instances, structural alterations along the edge of geographic atrophy were misinterpreted as RPE elevations that appeared to be DLSs associated with MNV. Otherwise, the graders correctly identified the more typical low-lying irregular PEDs as DLSs, and these OCT findings did correlate with MNV. Overall, structural OCT does a good job in the absence of OCT-A, but SS-OCT-A should be considered the gold standard for the detection of these subclinical neovascular lesions.[3,4,12]

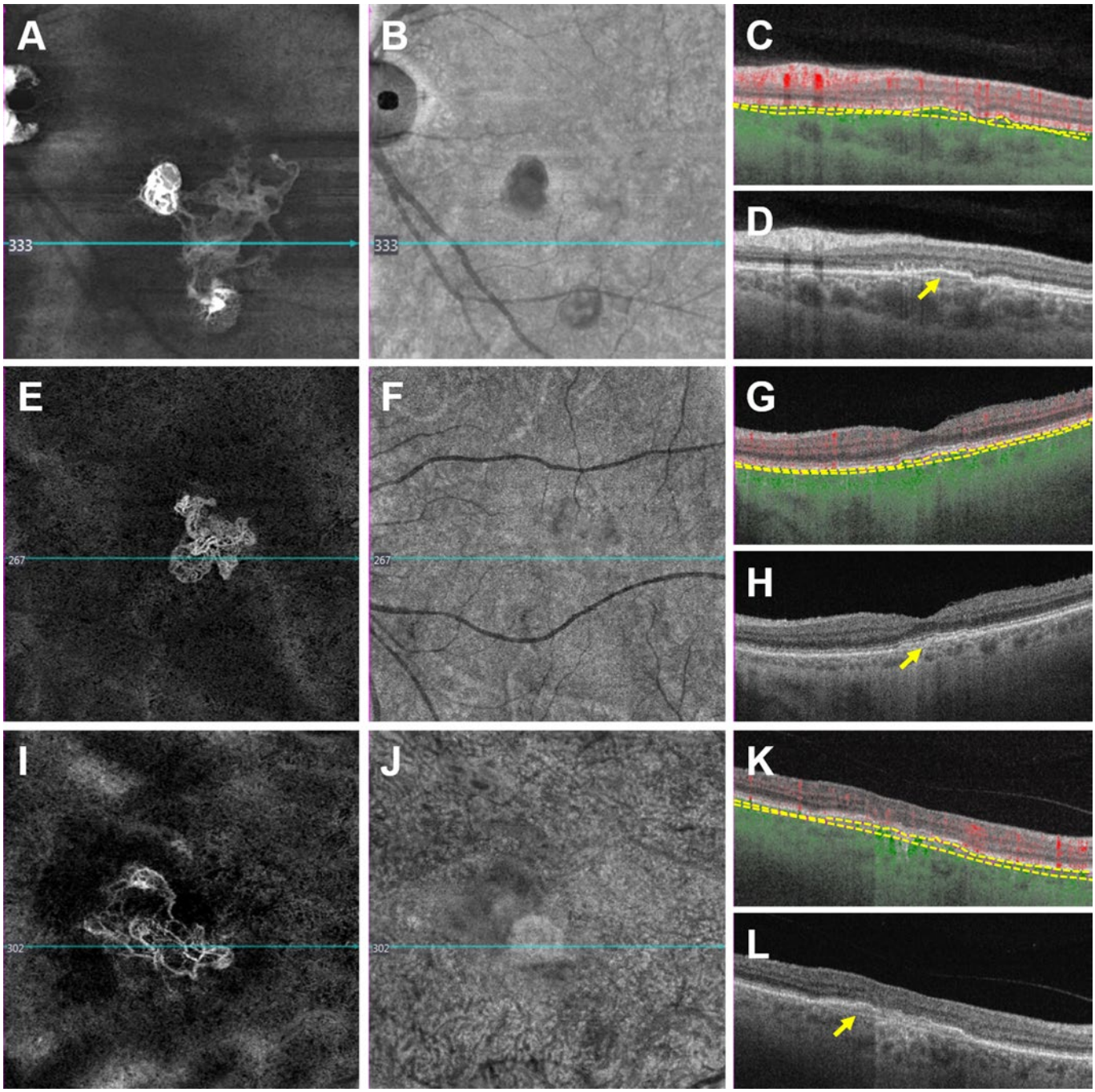

Figure 1. Subclinical macular neovascularization (MNV) identified by the presence of a double layer sign (DLS) on structural swept-source OCT (SS-OCT) images from 3 eyes without exudation. A, E, I: 6x6-mm en face angiographic image of MNV from a slab with segmentation boundaries extending from the retinal pigment epithelium (RPE) to the Bruch membrane (BM) showing CNV pattern; B,F,J: 6x6-mm en face structural images using the same slab as in panels A, E, and I; C, G, K: SS-OCT structural B-scans through the subclinical type 1 MNV with color-coded flow using red (top) for the retinal microvasculature and green (bottom) for flow under the RPE. The dashed lines represent the slab boundaries from the RPE to the BM. D, H, L: SS-OCT structural B-scans through the lesion showing DLS (arrow). A-D: Polypoidal choroidal vasculopathy with a branching vascular network associated and a DLS seen on the structural OCT image (arrow). E-H: Typical type 1 MNV with a DLS on the structural OCT image (arrow). I-L: Type 1 MNV with a DLS on the structural OCT image (arrow) and an area of evolving central macular atrophy.

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Cuticular Drusen: Risk Factors for Advanced AMD

Lawrence A Yannuzzi MD

Introduction

In 1977 Gass first described cuticular drusen (CD) as uniform, small (25-75 µm), translucent or yellow subretinal lesions densely clustered in the macula and in the midperiphery of the fundus. These lesions were shown to exhibit a "stars-in-the-sky" appearance with fluorescein angiography (FA). In 1985, Gass et al reported that CD were focal nodular thickenings of the retinal pigment epithelium (RPE) basal lamina. In 2000, Russel et al offered an alternative concept, suggesting that these drusen were cellular aggregations located between the basal lamina of the RPE and the inner collagenous layer of the Bruch membrane, similar to traditional medium and large soft drusen occurring in AMD. Thereafter, the term "cuticular drusen" became widely used to represent this clinical entity.

A recent study proposed a strict clinical definition of CD using available histopathology and current technology with multimodal imaging. These findings most notably demonstrated the need for OCT and fundus autofluorescence (FAF) to identify CD accurately with a high degree of sensitivity and specificity. Gass also reported that CD can become associated with an acquired vitelliform lesion (AVL), resulting from a loss of apposition between the photoreceptor tips and the RPE. Vitelliform detachments in patients with CD can resolve, leading to geographic atrophy (GA). Cohen et al reported macular neovascularization (MNV) in 31% of patients with CD and vitelliform detachment during a 24-month period of follow-up. In other reports, CD were also associated with GA and MNV. No known studies, to date, have examined the risk of progression to GA or MNV in eyes presenting with CD.

In the present study, we have examined eyes with CD longitudinally, analyzing the incidence and characteristics of GA and MNV to further understand the clinical significance of CD on macular function.

Purpose

CD have been associated with manifestations of AMD such as atrophy and neovascularization in the macula. In this study, eyes with CD were followed and investigated for the estimated 5-year risk of progression to sequelae of AMD such as GA and MNV.

Methods

A consecutive series of patients with CD were followed for development of GA and MNV. Whenever possible, they were also studied retrospectively. The patients with CD were categorized into 3 phenotypic groups. Phenotype 1: eyes had concentrated, densely populated CD in the macular and paramacular area; Phenotype 2: eyes showed scattered CD in the posterior fundus; and Phenotype 3: eyes showed CD mixed with large drusen (> 125 µm). The 5-year incidence of progression was then estimated using a Kaplan-Meier estimator.

Results

A total of 63 eyes from 38 patients (35 females with a mean age at presentation of 58.9 ± 14.2 years) were studied and followed for a mean of 40 ± 18 months. Thirteen patients had single eyes with GA (84.5%; 11/13) or MNV (15.5%; 2/13) in 1 eye at presentation and were subsequently excluded. GA developed in 19.0% of eyes (12/63); and MNV, in 4.8% of eyes (3/63). The cumulative estimated 5-year risk of GA and MNV was 28.4% and 8.7%, respectively. The estimated 5-year incidence of MNV or GA was 12.6%, 50.0%, and 51.6% in Phenotype 1, Phenotype 2, and Phenotype 3, respectively ($P = .0015$, log-rank test). No difference in risk was found in the development of GA or MNV ($P = .11$) between the subgroup of patients presenting with GA or MNV in their fellow eye and those with both eyes included.

Conclusions

When patients with CD are followed longitudinally, there is a significant risk of progression to GA or MNV for Phenotype 2 and Phenotype 3. Patients with CD are commonly first diagnosed in the fifth decade of life, and there is a female predominance. Clinicians should use multimodal imaging to detect and be aware of the risk of progression to manifestations of GA and MNV. These risks of GA and MNV suggest that patients with CD may be part of the overall spectrum of AMD.

Endophthalmitis and Pseudoendophthalmitis Following Intravitreal Injections

Distinguishing Between Infectious Endophthalmitis and Noninfectious Inflammation Following Intravitreal Anti-VEGF Injections

Harry W Flynn Jr MD and Stephen G Schwartz MD MBA

Endophthalmitis is a serious, vision-threatening condition that may occur following intravitreal injections.[1,2] The rate of infectious endophthalmitis after anti-VEGF injection is very low and appears to have fallen in recent years. According to the American Academy of Ophthalmology's IRIS Registry data (personal communication, David Parke MD, Sept. 2017), the rate of infectious endophthalmitis after anti-VEGF injections is approximately 0.005% and does not significantly vary among the three agents. At the Bascom Palmer Eye Institute, the rates were 0.005% (1 in 21,384) in 2016 and 0.004% (1 in 22,521) in 2017.[2] Recommendations for reducing rates of infectious endophthalmitis have been published.[3-5]

The rate of noninfectious inflammation is unknown, but based on clinical experience it is low. Noninfectious inflammation has been reported with all anti-VEGF agents,[6,7] but as least two major clusters have been associated with aflibercept. The first occurred shortly after the drug was approved in 2011, and the second occurred between September 2017 and May 2018.[8-10] The causes of both clusters are poorly understood, and it is not known if these cases were related to the drug itself, the vehicle, or the syringe.

The appearance of noninfectious inflammation may sometimes resemble that of infectious endophthalmitis. There are no definitive findings on history or examination that can completely distinguish between these two entities. Using the guidelines below, the examiner may establish a reasonable degree of certainty regarding the correct diagnosis. The major factors differentiating infectious from noninfectious cases (see Table 1) are the timing of the symptoms and the degree of inflammation. In general, infectious cases present earlier and have more severe inflammation, but there may be substantial overlap between these two entities. Infectious endophthalmitis typically presents within 24-48 hours of the injection, while noninfectious inflammation usually presents after several days. Infectious endophthalmitis is more likely to have eyelid edema, purulent discharge, severe conjunctival congestion, severe (3+ or more) cell and flare, fibrin, and hypopyon, although patients with noninfectious inflammation may have milder degrees of these as well.

The dilemma of distinguishing infectious from noninfectious inflammation has occurred in other ophthalmic procedures. With intravitreal triamcinolone, the steroid particles can resemble endophthalmitis but usually the two entities can be recognized.[11] With cataract surgery, toxic anterior segment syndrome (TASS) can sometimes resemble infectious endophthalmitis, but subtle differences can be identified.[12-13]

Table 1. Distinguishing Between Infectious Endophthalmitis and Noninfectious Inflammation After Anti-VEGF Agents

Characteristic	Infectious Endophthalmitis	Noninfectious Inflammation
Timing of onset	Usually 1-2 days following injection	Several days following injection
Pain	Usually mild or moderate	None or mild
VA on presentation	May be a severe decrease	Mild to moderate decrease
Corneal edema	May be moderate or severe	None or mild
Anterior chamber	Usually moderate to severe cell and flare	May have mild cell or flare
Fibrin	Always present	Usually none
Hypopyon	Usually present	Usually absent
Vitreous	Marked cell/opacities	Mild to moderate cells
Management	Tap and inject or pars plana vitrectomy	Topical steroids
Prognosis	Variable with specific organism but generally poor	Generally good

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Anterior Segment Complications of Multiple Intravitreal Injections

John T Thompson MD

I. Introduction

The dramatic rise in repeated intravitreal injections (3.457 million in US Medicare recipients in 2017) has led to recognition of common, as well as some rare, but significant, anterior segment complications. Intravitreal injection has become the most common intraocular surgical procedure in ophthalmology and is one of the most common procedures in all of medicine.

II. Subconjunctival Hemorrhage

A. Incidence 11.2% in one study. Elevated systolic blood pressure and pulse rate were associated with increased risk of subconjunctival hemorrhage.[1]

B. May cause increased irritation following intravitreal injection

C. Patients on anticoagulants appear at increased risk.

D. Often leads to unnecessary weekend / night calls to office

III. Corneal Abrasion

A. Incidence varies somewhat by injection technique but was 0.15% in a study.[2]

B. Can result from abrasion from lid speculum, proparacaine-soaked pledget contacting cornea, movement with needle close to eye, or self-induced trauma in anesthetized cornea.

C. Diabetic patients and those with basement membrane dystrophies are most susceptible.

IV. Corneal or Retinal Perforation due to Sudden Patient Movements

A. Incidence 0.003% in my experience

B. Sudden patient movement is especially problematic in elderly patients with early dementia.

C. Sudden ocular movement: Recall that ocular saccades are the fastest movement in the human body.

V. Hyphema

A. Incidence 0.02% in my series

B. Anterior injection site through ciliary body

C. Anticoagulant use is a risk factor.

D. May mimic signs of endophthalmitis

VI. Noninfectious Uveitis

A. Can be difficult to distinguish from infectious endophthalmitis but inflammation is milder in anterior segment

B. 0.73% rate of uveitis in eyes receiving anti-VEGF injections compared to controls with 0.37% ($P < .01$)[3] from the 5% Medicare database

C. Recent cluster with aflibercept has been reported.

VII. Endophthalmitis

A. 0.62% incidence of endophthalmitis in eyes receiving anti-VEGF injection compared to 0.10% in controls ($P < .01$), with a per-injection risk of endophthalmitis of 0.08% in excess of controls.[3]

B. Cox hazard ratio of 2.29 for endophthalmitis within 40 days of cataract surgery compared to eyes without cataract surgery ($P < .05$) in a 5% sample of Medicare beneficiaries and the increased risk of endophthalmitis persisted > 40 days following surgery (hazard ratio 3.65, $P < .01$) due to continued intravitreal injections.[4]

VIII. Acute Cataract From Lens Damage

A. Incidence of 0.2% in MARINA[5] trial and 0% in ANCHOR[6] trials

B. Typically involves posterior capsule with focal cataract that progresses rapidly to diffuse lens opacity[7]

IX. Cataract Surgery and Anti-VEGF Injections

A. Cataract surgery did appear to be relatively safe in eyes that received anti-VEGF injections in the Phase 3 MARINA and ANCHOR trials.[8]

B. Surgery for removal of retained lens fragments was 2.26 times more likely within 28 days in eyes with prior intravitreal injections ($P < .05$).[4]

C. Another study found cataract surgery complications in 3% with prior intravitreal injections vs. 0% of eyes without prior intravitreal injections ($P = .03$).[9]

D. Intravitreal injections can cause direct posterior capsule damage if injection is too anterior or angled anteriorly.

E. Repeated intravitreal injections displace / disrupt vitreous anatomy in the vitreous base and may damage zonules. This likely explains a majority of cataract surgery complications.

F. No evidence of posterior capsule damage in any of the 4 cases of cataract surgery complications following intravitreal injections I have observed

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New Instrumentation

David R Chow MD

NOTES

Case Studies and Management Panel

Panel Moderator: Dean Eliott MD

Panelists: Giampaolo Gini MD, Carlos Mateo MD, Kirk H Packo MD, Adrienne Williams Scott MD, Paulo E Stanga MD, Paul E Tornambe MD

NOTES

Analysis of the Intestinal Microbiome in Retinal Diseases

Sebastian Wolf MD PhD and Martin Zinkernagel MD PhD

The microbes within the human gastrointestinal tract are referred to as the intestinal gut microbiome. The gut microbiome plays a major role in the digestion of food and influences global metabolism of the human body. The gut microbiome contains more than 10 times more cells than the human body, and the genes encoded by the bacteria in the gut outnumber the human genes by a factor of 100. It is a complex ecosystem of more than 100 trillion microbes, which influence human physiology, metabolism, nutrition, and immune function.

In recent years, the intestinal gut microbiome has become the subject of extensive research, and our knowledge of the resident species and their potential functional capacity is rapidly growing. Changes in microbiota composition can potentially modulate host metabolism and may act as source of inflammation and disease. Recent studies have shown that the gut microbiota may contribute to metabolic and inflammatory diseases, such as cardiovascular disease, atherosclerosis, chronic gastrointestinal diseases, type 2 diabetes, and obesity. A recent study suggests that the gut microbiome triggers autoimmunity in the eye through activation signals to retina-specific T cells. Given the link between AMD and diet, the composition of the gut microbiota may also influence AMD development and progression.

Recently, we could demonstrate in a small pilot that AMD patients have only a moderate degree of gut bacterial dysbiosis, but functional annotation analyses indicated that specific genes involved in individual metabolic pathways are enriched or decreased in patients with AMD. In a confirmatory study we have been able to reproduce an altered ration of *Firmicutes* to *Bacteroidetes* in the gut microbiota of AMD patients.

In patients with retinal artery occlusion (RAO), which is closely associated with atherosclerosis, we have observed associations between RAO and microbiome composition. Previous studies have identified a higher abundance of *Actinobacteria* in the gut of patients with symptomatic atherosclerosis, which is in keeping with our data.

The human intestinal gut microbiome evolves throughout life and appears to play an important role in both health and various diseases, including retinal diseases. In a healthy state, the intestinal microbiome has many positive functions, including metabolism of food, protection of a host from pathogenic invasion, and modulation of the immune system. Alterations of the human gut microbiome may interact with the human metabolism and result in pathological conditions, such as arteriosclerosis and AMD and other retinal diseases, although the specific contribution of the gut microbiota to these diseases is unclear. Therefore, further studies are needed to confirm functional differences in the gut microbiome by correlating metabolic profiles and quantification of messenger RNA in patients with retinal diseases.

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New Concepts in Classifying Myopic Macular Degeneration

Tien Y Wong MBBS

Myopia and Myopic Macular Degeneration

Myopia is a common problem worldwide, affecting 25%-40% of adults aged > 40 years.[1] Myopic macular degeneration (MMD), sometimes known as pathologic myopia (PM), myopic maculopathy, or degenerative myopia (used interchangeably here), is a possible consequence of myopia, particularly in eyes with high myopia (typically defined as spherical equivalent of at least –6.0 D).[2-4]

MMD is characterized by progressive elongation of the globe and abnormal choroidal vasculature (mainly in eyes with posterior staphyloma), with additional degenerative changes seen in the retina. MMD is estimated to affect up to 3% of the global population and is a particularly frequent cause of vision impairment and blindness in the young working-age population, thus having a considerable social and economic impact.

Myopic CNV

One of the most serious complications of MMD is myopic choroidal neovascularization (mCNV), which often leads to a sudden onset but progressive decline in central vision and is associated with a poor prognosis unless treated. It has been reported that approximately 5%-11% of individuals with MMD will develop mCNV, although this may be an underestimate.[2,3] The interrelationship between the degree of myopia and the development and progression of MMD and mCNV is not fully understood.

The introduction of intravitreal anti-VEGF therapies for patients with mCNV has had a major impact on the management of these patients, and its efficacy and safety is now supported by 2 Phase 3 randomized clinical trials using ranibizumab[5] and aflibercept.[6]

Classification of Myopic Macular Degeneration

There continues to be a lack of a standardized classification system for MMD. Clinically, typical changes in MMD include the following:

- Peripapillary atrophy
- Thinning of the retinal pigment epithelium (RPE) and choroid
- Lacquer cracks in the Bruch membrane
- Subretinal hemorrhage
- Posterior staphyloma
- mCNV

Avila et al described a severity pattern (M0 to M5) for MMD, which has been used in some studies to characterize patients.[7]

More recently, Ohno-Matsui et al have also proposed an international photographic classification and grading system for MMD (0-4; see Table 1).[8] This system has been adopted by different groups.

Table 1

Classification of MMD	Stage	Features	
Avila et al[7]	M0	Normal-appearing posterior pole	
	M1	Choroidal pallor and tessellation (Reduced RPE pigmentation means the choroidal vessels can be seen through the retina.)	
	M2	Choroidal pallor and tessellation with posterior staphyloma	
	M3	Choroidal pallor and tessellation with posterior staphyloma and lacquer cracks	
	M4	Choroidal pallor and tessellation with lacquer cracks, posterior staphyloma, and focal areas of deep choroidal atrophy	
	M5	Posterior pole with large geographic areas of deep chorioretinal atrophy and "bare" sclera	
Ohno-Matsui et al[8]	0	No macular lesions	"Plus" lesions: • Lacquer cracks • CNV • Fuchs spot
	1	Tessellated fundus	
	2	Diffuse chorioretinal atrophy	
	3	Patchy chorioretinal atrophy	
	4	Macular atrophy	

Nevertheless, important clinical questions remain:

- How do we define tessellated fundus (Category 1)?
- How do we differentiate tessellated fundus from diffuse CRA (Category 2)?
- How do we define diffuse CRA (Category 2) and patchy CRA (Category 3)?
- How does macular atrophy (Category 4) develop?

Classification of mCNV

mCNV appears as "classic" pattern of CNV on fluorescein angiography (FA), as a well-defined lesion with hyperfluorescence in the early phases and dye leakage during the later phases.[9] However, not all eyes show fluorescein leakage, and if a hemorrhage is present this can interfere with FA; in these cases, indocyanine green angiography (ICGA) may aid in differentiating the lesion and provide a more accurate location.

Spectral domain OCT (SDOCT) can provide useful information on the presence and stage of mCNV. During the active stage, a highly reflective dome-shaped projection above the RPE is typically visible (type 2 CNV), and subretinal as well as intraretinal fluid may be detectable. During the scarring stage, only the surface of the CNV shows high reflectivity. Finally, in the atrophic stage the CNV flattens, but an increase in surrounding choroidal reflectivity is observed due to chorioretinal atrophy.

Is FA necessary for diagnosis of mCNV? Some studies show that when compared to FA, SD-OCT alone was found to be inferior in detecting signs of mCNV activity, suggesting that FA should be performed in any suspected case of mCNV.

Recent studies have used OCT angiography to characterize presence, severity, and treatment response of mCNV.

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Affordable Stem Cell Therapies

Edwin M Stone MD PhD

Major Concepts and Definitions

- The neurons of the human retina cannot renew themselves if they die.
- Outer retinal diseases like AMD and rare inherited diseases like Stargardt disease and retinitis pigmentosa usually spare the inner retina and optic nerve even very late in the disease. This raises the possibility of replacing outer retinal neurons by transplantation.
- Mature neurons (eg, from human donor eyes) cannot survive any attempts at isolation or transplantation (a 25-year-old idea).[1]
- Some fetal retinal cells will survive isolation,[2] but (in our hands) if expanded in culture to the point that multiple patients can be treated, they do not give rise to mature photoreceptor cells following transplantation.
- Embryonic cells *can* be differentiated into mature photoreceptors, but they are not immunologically matched to the recipient and this process has some ethical barriers.[3-4]
- Induced pluripotent stem cells (iPSCs) *can* be differentiated into mature photoreceptors but will not be immunologically matched to the recipient unless they are created from the tissue of the patient for whom they are intended.[5-8]
- Patient-derived iPSCs *can* be differentiated into mature photoreceptors *and* be completely immunologically matched to the recipient.[9] However, the latter requires CRISPR-based gene editing and extensive post-correction validation to insure that no harmful mutations are introduced during reprogramming, gene editing, or differentiation.[10]
- Injection of unsupported cells into the subretinal space is associated with very low rates of survival and integration (less than 5%).[11]
- Transplantation of retinal progenitor cells imbedded within a dissolvable biopolymer support into the subretinal space is associated with greater than 75% survival.[11-13]
- The median total net worth of a household in the United States (including home equity) is less than $100,000.[14] Without some type of governmental or actuarial wealth redistribution, few people will be able to receive such a transplant unless the total cost of the treatment falls below $100,000.
- Robotics can increase the throughput (and decrease the cost) of a GMP stem cell facility (and the transplantable cells it produces) more than 50-fold.

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ZEBRA Study Executive Summary

Alan L Wagner MD, Haley S D'Souza, Kapil G Kapoor MD

Summary Statement

Ziv-aflibercept is a safe and effective alternative to currently available anti-VEGF medications in treating patients with neovascular AMD. In non–treatment naïve eyes with BCVA ≤20/200, ziv-aflibercept is noninferior with statistical significance with respect to visual acuity, central foveal thickness, injection interval duration, and complication rate when compared to aflibercept and bevacizumab.

Abstract

Purpose

The purpose of this study is to determine the safety and efficacy of ziv-aflibercept in treating neovascular AMD.

Methods

This is an IRB-approved prospective, randomized, case-control study of patients undergoing treatment for neovascular AMD. Inclusion criteria were previous therapy with at least 3 intravitreal anti-VEGF treatments, BCVA of ≤20/200 in the treatment eye, and better vision in the contralateral eye. The treatment group received 1.25 mg/0.05mL intravitreal ziv-aflibercept, while the control group continued their existing anti-VEGF regimen.

Results

Forty-nine patients completed a mean of 6 months of follow-up (range: 3-9). Mean baseline BCVA was 1.62 ± 0.44 logMAR (Snellen equivalent: CF 6 ft) in the control group (n = 25), and 1.78 ± 0.32 logMAR (Snellen equivalent: CF 5 ft) in the treatment group (n = 24). Mean change in BCVA was 0.03 logMAR and 0.02 logMAR in the control and treatment groups, respectively (P = .94). Baseline CFT in the control and treatment groups was 265 ± 84 μm and 245 ± 81 μm, respectively, and mean change in CFT was 28 μm and 18 μm, respectively (P = .72). Ziv-aflibercept did not demonstrate any adverse effects during the study.

Conclusion

Ziv-aflibercept is a viable alternative to currently available anti-VEGF medications in treating patients with neovascular AMD, and it is noninferior in terms of anatomy, function, and complication rate. Due to ziv-aflibercept's efficacy and relatively lower cost, it may represent and important cost-effective addition to current anti-VEGF treatment options.

Medical Retina Panel Discussion

Panel Moderator: Jose S Pulido MD MS

Panelists: Usha Chakravarthy MBBS PhD, Jay K Chhablani MBBS, Karl G Csaky MD, James C Folk MD, Lihteh Wu MD, Seung Young Yu MD PhD

NOTES

Video Surgical Complications—What Would You Do?

Silicone Oil

Asheesh Tewari MD

Retinal Detachment Surgery

Andrew A Chang FRANZCO PhD

Perfluoron

Andre V Gomes MD

Anesthesia

Daniele Tognetto MD

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David H Abramson MD FACS
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Nisha Acharya MD
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Anita Agarwal MD
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Lloyd P Aiello MD PhD
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Carl C Awh MD
Bausch + Lomb: C

Sophie J Bakri MD
Allergan: C
Genentech: C
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Zeiss: C

Alay S Banker MD
Santen: C

Irene A Barbazetto MD
Allergan: C
Genentech: C

Charles C Barr MD FACS
None

Caroline R Baumal MD
Genentech: C
pSivida: C

Audina M Berrocal MD
Alcon Laboratories Inc.: C
DORC International, bv/Dutch Ophthalmic, USA: C,L
Phoenix: C
Visunex: C
Zeiss: C

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

Cagri G Besirli MD
iRenix Medical: C,O,P
ONL Therapeutics: P

Susanne Binder MD
Carl Zeiss Meditec/Oberkochen: C

Barbara Ann Blodi MD
None

David S Boyer MD
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Neil M Bressler MD
Alkeus: S
Bayer Healthcare Pharmaceuticals: S
Chiltern: S
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Samsung Bioepis: S

Susan B Bressler MD
Bayer Healthcare Pharmaceuticals: S
Boehringher Ingleheim: S
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David M Brown MD
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David J Browning MD PhD
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Zeiss: O

Alexander J Brucker MD
DRCR.net: S
Genentech: S
National Eye Institute: S
Ophthotech: O,S

Antonio Capone Jr MD
Alcon Laboratories, Inc.: S
Aura Biosciences: S
Broadspot: O
FocusROP: O
GENENTECH: S
Iconic Therapeutics: S
interVIEW: O,P
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Spark Therapeutics: C
ThromboGenics, Inc.: S

Colleen M Cebulla MD PhD
NIH: S
Ohio Lions Eye Research Foundation: S
Ohio Ophthalmological Society: L

Usha Chakravarthy MBBS PhD
Allergan: C
Carl Zeiss Meditec: L
Heidelberg Engineering: L
Roche Diagnostics: L

R V Paul Chan MD
Alcon Laboratories Inc.: C
Allergan: C
Bausch + Lomb: C
Visunex Medical Systems: C

Andrew A Chang MBBS
Alcon Laboratories Inc.: C
Allergan Inc.: C,L
Bayer Healthcare Pharmaceuticals: C,L,S
Novartis Pharma AG: C

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

Gemmy Chui Ming Cheung MB BChir FRCOphth
Allergan: L
Bayer Healthcare Pharmaceuticals: C,L,S
Novartis, Alcon Pharmaceuticals: C,L,S
Topcon Medical Systems Inc.: S

Emily Y Chew MD
None

Jay K Chhablani MBBS
None

David R Chow MD
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

Carl C Claes MD
Alcon Laboratories Inc.: C

Jason I Comander MD PhD
Beam Therapeutics: C
Blue Cross Blue Shield: C
Editas Medicine: C
Gensight: C

Karl G Csaky MD
Acucela: C
AGTC: C
Allergan: C
Astellas: C
Genentech: C,L
Heidelberg Engineering: C
Merck & Co. Inc.: C
Ocular Therapeutix: C
Ophthotech: C
Regeneron Pharmaceuticals Inc.: C

Catherine A Cukras MD PhD
None

Emmett T Cunningham Jr MD PhD MPH
None

Janet Louise Davis MD
AbbVie: C
Allergan: C

Diana V Do MD
Bayer Healthcare Pharmaceuticals: C
Genentech: C
Novartis: C
Regeneron Pharmaceuticals Inc.: S
Santen Inc.: C

Kimberly A Drenser MD PhD
Allergan: C
FocusROP: O
Genentech: C
Retinal Solutions: O
Spark Therapeutics: C

Pravin U Dugel MD
Acucela: C
Aerie Pharmaceutical: C
Aerpio: C,O
Alcon Laboratories, Inc.: C
Alimera Sciences, Inc.: C,O
Alimera: O,C
Allegro Ophthalmics, LLC: C,O
Allergan: C
Amgen: C
Annidis: C,O
ArcticDx, Inc.: C
Bausch+Lomb: C
Beyeonics: C
Boehringer Ingelheim Pharma GmbH: C
Boehringer Ingelheim: C
Byeonics: C
Changdu Kanghong Biotechnology: C
Chengdu Kanghong Biotechnology: C
Clearside Biomedical: C,O
Digisight: C,O
DOSE Medical: C
GENENTECH: C
Graybug Vision: C
Irenix: C,O
Kodiak Sciences: C
Lux BioScience: C
Macusight: C
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
PSivida Corporation: C
Regeneron Pharmaceuticals, Inc.: C
Regeneron: 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

Jay S Duker MD
Allergan: C
Aura Bio: C
Carl Zeiss Meditec: C,S
EyePoint Pharma: C
Helio Vision: C
Hemera Biosciencies: O
Hoffman La Roche Ltd.: C
Novartis, Alcon Pharmaceuticals: C
OptoVue: C,S
Santen Inc.: C
Sesen Bio: C
Topcon Medical Systems

Claus Eckardt MD
None

Ehab N El Rayes MD PhD
Alcon Laboratories Inc.: C
Bayer Healthcare Pharmaceuticals: C
DORC International, bv/Dutch Ophthalmic, USA: C
Johnson & Johnson: C
Medone Surgical: P
Novartis Pharmaceuticals Corp.: C

Dean Eliott MD
Aldeyra Therapeutics: C
DORC International, bv/Dutch Ophthalmic, USA: C
Helio Vision: O

Nicole Eter MD
Alimera Sciences Inc.: L,C
Allergan: C,L
Bayer Healthcare Pharmaceuticals: C,L,S
Novartis Pharmaceuticals Corp.: C,L,S
Roche: C

Amani Fawzi MD
None

Philip J Ferrone MD
Allergan: S
ArcticDx Inc.: O
Genentech: C,S
Mckesson: C
Novartis Pharma AG: S
Regeneron Pharmaceuticals Inc.: S
Regenixbio: C

Yale L Fisher MD
None

Harry W Flynn Jr MD
None

James C Folk MD
IDx: O

William R Freeman MD
Allergan: C
Genentech: C
Nanovision: C,O
Spinnaker Biosciences: C

K Bailey Freund MD
Allergan: C
Genentech/Roche: S
Heidelberg Engineering: C
Novartis, Alcon Pharmaceuticals: C
Optovue: C
Zeiss: C

Mark C Gillies MD PhD
Allergan: C,L,S
Bayer Healthcare Pharmaceuticals: C,L,S
Novartis Pharmaceuticals Corp.: C,L,S
Opthea: C
Roche Diagnostics: C

Giampaolo Gini MD
None

Michael Goldbaum MD MS
None

Andre V Gomes MD
Allergan: C
DORC International, bv/Dutch Ophthalmic, USA: C
Novartis Pharmaceuticals Corp.: C

Evangelos S Gragoudas MD
Aura Pharmaceuticals: C
Iconic Therapeutics: C
Ocata Therapeutics: C
Valeant: P

M Gilbert Grand MD
None

Jeffrey G Gross MD
Acucela: S
Genentech: S
Jaeb Center for Health Research: S
Ohr Pharmaceutical: S
Regeneron: S

Robyn H Guymer MBBS PhD
Bayer Healthcare Pharmaceuticals: C
Genentech: C
Novartis Pharma AG: C

Julia A Haller MD
Aura Biosciences: C
Celgene: O
KalVista: C
Lowy Medical Research Institute: C
Novartis Pharmaceuticals Corp.: C
Spark Therapeutics: C

Dennis P Han MD
Acucela Inc.: S
Alcon Research Ltd.: S
Appelis: C
Aura Sciences: C
FlowOne LLC: C
Opthea: C

Mary Elizabeth Hartnett MD FACS
Knights Templar Eye Foundation: C
Lippincott Williams and Wilkins: P
NIH/NEI: S
Novartis: S
Parexel: S

Sohail J Hasan MD PhD
None

Tarek S Hassan MD
Alcon Laboratories, Inc.: C
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 Corporation: C
Ocugenix: C
Oculus, Inc.: C,O
Regeneron Pharmaceuticals, Inc.: C
Surgicube: C
Vitreq: C

Jeffrey S Heier MD
4DMT: C
Adverum: C
Aerie Pharmaceuticals, Inc.: C
Aerpio: C,S
Allegro: C
Apellis: C,S
Asclepix: C
Bayer Healthcare Pharmaceuticals: C
Beaver-Visitec International, Inc.: C
Chengdu Kanghong Biotech: C
Corcept: S,C
Daiichi: C,S
Galecto: C
GENENTECH: C,S
Genzyme: S
Helio: C
Hemera: C,S
irenix: C
Janssen R&D: S
Kodiak: C
Notal Vision, Inc.: C
Novartis Pharma AG: C
Ocular Therapeutix: C,O
Ocunexus: C
Ophthotech: S
Optos, Inc.: C
Optovue, Inc.: S
Quark Pharmaceuticals: C
Ra Pharmaceuticals: C
Regeneron Pharmaceuticals, Inc.: C,S
Regenxbio: C,S
Santen, Inc.: C
Scifluor: C,S
Shire: C
Stealth Biotherapeutix: C
ThromboGenics, Inc.: C
Tyrogenex: C,S

Allen C Ho MD
Aerpio: 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
DigiSight Technologies, Inc.: C,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

Frank G Holz MD
Alcon Laboratories Inc.: C
Allergan: S,C
Apellis: C
Bayer Healthcare Pharmaceuticals: S,C,L
Boehringer-Ingelheim: C
Centervue: S
Genentech: S,C
Heidelberg Engineering: S,C
Hoffman La Roche Ltd: C,S
LIN Bioscience: C
Nightstar: S
Novartis Pharmaceuticals Corporation: C,L,S
Optos: S

G Baker Hubbard MD
None

Mark S Humayun MD PhD
1Co., Inc.: C,O,P
Acucela: C,L
Alcon Laboratories, Inc.: C,L
Allergan: C
Clearside: C
Duke Eye Center: P
Eyemedix: C,O,P,S
IRIDEX: P
John Hopkins University: P
oProbe: C,O,P
Reflow: C,O,P
Regenerative Patch Technologies (RPT): C,O,P
REPLENISH: C,O,P
Santen, Inc.: C
Second Sight Medical Products, Inc.: C,O,P
University of Southern California: E,P

Gustavo Matias Huning MD
None

Glenn J Jaffe MD
Abbott: C
Heidelberg Engineering: C
Neurotech: C
Novartis Pharma AG: C
pSivida: C
Regeneron Pharmaceuticals Inc.: C

Lee M Jampol MD
None

Mark W Johnson MD
Hoffman-LaRoche: S
Ohr: C
Pfizer Inc.: C
Tyrogenex: C

Kazuaki Kadonosono MD
None

Peter K Kaiser MD
Aerpio: C
Alcon Laboratories, Inc.: C,L
Allegro: C
Bayer Healthcare Pharmaceuticals: C,L
Biogen Inc: C
Digisight: C
Kanghong: C
Novartis Pharmaceuticals Corporation: C,L
Ohr: C,O
Omeros: C
Ophthotech: C,L
Regeneron Pharmaceuticals, Inc.: C,L
Santen: C
SciFluor Lide Sciences: C
Shire: C
Thrombogenics: C

Amir H Kashani MD PhD
Alimera Sciences Inc.: C
California Institute for Regenerative Medicine: S
Carl Zeiss Meditec: S,L
National Eye Institute: S
Regenerative Patch Technologies: S

Arshad M Khanani MD
Aerpio: C,S
Alcon Laboratories Inc.: C,S
Alimera Sciences Inc.: C
Allergan: C,L,S
Digisight: S
Genentech: C,L,S
Novartis Pharmaceuticals Corp.: C,L,S
Ophthotech: S
Opthea: S
Santen Inc.: C
ThromboGenics Inc.: C,S

Rahul Khurana MD
Allergan Inc.: C,S
Clearside Biomedical: S
Genentech: C,L
Google: C
Regeneron: C,L
Santen Inc.: C,S

Judy E Kim MD
Alimera Sciences Inc.: C
Genentech: C
Notal Vision Inc.: S
Notal Vision: C
Optos Inc.: S

Szilard Kiss MD
Adverum: C
Alimera Sciences Inc.: C
Allergan: C
Genentech: C
Optos Inc.: C
Regeneron Pharmaceuticals Inc.: C
RegenxBio: C
Spark: C

John W Kitchens MD
Alcon Laboratories, Inc.: C
Alimera Sciences, Inc.: C
Allergan: C
Bayer Healthcare Pharmaceuticals: C
Carl Zeiss Meditec: C
DORC International, bv/Dutch Ophthalmic, USA: C
GENENTECH: C
Johnson & Johnson: C
Notal Vision, Inc.: C
Regeneron Pharmaceuticals, Inc.: C
Vortex Surgical: C

Frank H Koch MD
None

Baruch D Kuppermann MD PhD
Aerpio: C
Alcon Laboratories, Inc.: C,S
Alimera Sciences, Inc.: C,S
Allegro: C,S
Allergan: C,S
Apellis: S
Catalyst: C
Cell Care: C
Dose: C
Eyedaptic: C,O
GENENTECH: C,S
Glaukos Corporation: C
GlaxoSmithKline: S
Ionis: S
J-Cyte: S,C
Novartis, Alcon Pharmaceuticals: C
Ophthotech: C,S
Regeneron Pharmaceuticals, Inc.: C,S
SciFluor: C
ThromboGenics, Inc.: S

Geeta A Lalchandani-Lalwani MD
Genentech: C
Novartis Pharma AG: C
Regeneron Pharmaceuticals Inc.: C

Jennifer Irene Lim MD
Alcon Laboratories, Inc.: C
Alimera Sciences, 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
Ohr: S
Ophthea: C
pSivida: C
Quark: C
Regeneron Pharmaceuticals, Inc.: S
Santen, Inc.: C
Second Sight Medical Products, Inc.: S

Anat Loewenstein MD
Allergan: C
Bayer Healthcare Pharmaceuticals: C
Notal Vision Inc.: C
Novartis Pharmaceuticals Corp.: C

Brandon J Lujan MD
BioTime: C
Carl Zeiss Meditec: S
CellCure: C
Genentech: C,S
Optovue: S
University of California, Berkeley: P

Michael F Marmor MD
None

Daniel F Martin MD
None

Carlos Mateo MD
Allergan: C
Bausch + Lomb: C

Colin A McCannel MD
Allergan: S
DORC International, bv/Dutch Ophthalmic, USA: C,L
Genentech: S

Tara A McCannel MD
None

William F Mieler MD
None

Joan W Miller MD
Bausch + Lomb: C
Genentech/Roche: C
Kalvista Pharmaceuticals: C
Lowy Medical Research Institute Ltd.: S
ONL Therapeutics LLC: C,O,P
Valeant Pharmaceuticals: P

Yuki Morizane
None

Prithvi Mruthyunjaya MD
Castle Biosciences Inc.: C
Optos Inc.: C
Santen Inc.: C
Spark: C

Timothy G Murray MD MBA
None

Priya Narang MS
None

Quan Dong Nguyen MD
AbbVie: C
Bayer Healthcare Pharmaceuticals: C
Genentech: C
Regeneron Pharmaceuticals Inc.: C
Santen Inc.: C

Masahito Ohji MD
Abbvie: L,S
Alcon Laboratories, Inc.: C,L,S
Allergan: C
Bayer Healthcare Pharmaceuticals: C,L,S
Carl Zeiss Meditec: L
Hoya: S
Kowa-Soyaku pharmaceutical: L
Novartis Pharmaceuticals Corporation: C,L,S
Otsuka Pharmeceutical: L,S
Pfizer, Inc.: L,S
R-E Medical: L
Santen, Inc.: C,L,S
Senju Pharmaceutical: L,S

Kyoko Ohno-Matsui MD
None

Andrew J Packer MD
None

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

Barbara Parolini MD
None

Grazia Pertile MD
None

Dante Pieramici MD
Aerpio: S
Allegro: S
Allergan: S
Genentech: C,S
Kodiac: C
Novartis: C
Regenerative Patch: S
Regeneron Pharmaceuticals Inc.: C,L,S
Santen Inc.: S

John S Pollack MD
Covalent Medical: O
DORC International, bv/Dutch Ophthalmic, USA: C
Genentech: C,S
Notal Vision Inc.: C,O
Novartis Pharma AG: C
Vestrum Health: O

Jonathan L Prenner MD
Alcon Laboratories Inc.: C

Jose S Pulido MD MS
Lagen: O,P

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
Notal Vision Inc.: C,S
Novartis Pharmaceuticals Corp.: C,S
Regeneron Pharmaceuticals Inc.: S
Shire: C

Elias Reichel MD
Akorn: P
Boston Image Reading Center: O
Eyemax: O
GENENTECH: C
GSK: C
Hemera Biosciences: O
Iconic Therapeutics: C,O
Lutronics: C,O
NewGen Biopharma: C,O
Nightstar: C
Ocular Instruments Inc: C,P
Ophthotech: C
Panoptica: C,O
pSivida: C
Regeneron Pharmaceuticals, Inc.: C,L,O
Spark Therapeutics: C,L
Theratechnologies: 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
Boehringer Ingelheim: C
CellView: C
Clarity: C
Diopsys Inc.: C
Genentech: S
Glaucohealth: C
Guardion Health: C
Nano Retina: C
Ocata: C
OD-OS: C
Opticology: O
Optovue: C,P
Regeneron Pharmaceuticals Inc.: 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
Tyrogenex: C,S
Unity Biotechnology: C

Edwin Hurlbut Ryan Jr MD
Alcon Laboratories Inc.: P

Srinivas R Sadda MD
Allergan: C,S
Carl Zeiss Meditec: C,S
Centervue: C
Genentech: C,S
Heidelberg Engineering: C
Iconic: C
Novartis Pharma AG: C
Optos Inc.: C,S
ThromboGenics Inc.: C
Topcon Medical Systems Inc.: L

Jose A Sahel MD
Banque Publique d'Investissement: S
Chronocam: O
Chronolife: O
ERC Synergy "Helmholtz": S
Foundation Fighting Blindness: S
Genesignal: C
GenSight Biologics: C
LabEx Lifesenses (ANR-10-LABX-65): S
Pixium Vision: C

Reginald J Sanders MD
None

David Sarraf MD
Allergan: S
Amgen: C
Bayer Healthcare Pharmaceuticals: C
Genentech: C,S
Heidelberg Engineering: S
Novartis Pharmaceuticals Corp.: L
Nuvelution: C
Optovue: C,L,S
Regeneron Pharmaceuticals 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: S,C
Regeneron Pharmaceuticals Inc.: S

Ursula M Schmidt-Erfurth MD
Boehringer Ingelheim: C
Genentech: C
Novartis Pharma AG: C
Roche Diagnostics: C

Adrienne Williams Scott MD
Allergan: C

Ingrid U Scott MD MPH
Thrombogenics: C

Hatice N Sen MD
None

Chirag P Shah MD MPH
Alimera Sciences Inc.: S
Allergan: S
Ellex: L,S
Genentech: S
Johnson & Johnson: S
National Eye Institute: S
NeoVista Inc.: S
Novartis, Alcon Pharmaceuticals: S
Ophthalmic Consultants-Boston: E
Regeneron Pharmaceuticals Inc.: C,S

Gaurav K Shah MD
Allergan: C,S
Bausch + Lomb: L
DORC International, bv/Dutch Ophthalmic, USA: S
Regeneron Pharmaceuticals Inc.: C,L

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
Mallinckrodt Pharmaceuticals: L
Optos, Inc.: S
psivida: C
Regeneron Pharmaceuticals, Inc.: L,S
Santen, Inc.: C
Spark Therapeutics, Inc.: C

Lawrence J Singerman MD
Aerpio: S
National Eye Institute: S

Rishi P Singh MD
Alcon Laboratories Inc.: C,S
Apellis: C,S
Genentech: C,S
Optos Inc.: C
Regeneron Pharmaceuticals Inc.: C,S

Jason S Slakter MD
Aura: S
Bayer HealthCare: L,S
Genentech: C,S
Gilead Sciences: S
GlaxoSmithKline: S
Johnson & Johnson: C,S
Mylan: S
Ohr Pharma: E,O,S
Regeneron Pharmaceuticals: C,S
Roche: S
Samsung: S
Sanofi-Aventis: S
SKS Ocular LLC: O

Elliott H Sohn MD
DORC International, bv/Dutch Ophthalmic, USA: C
Oxford Biomedica: S
Sanofi Fovea: S

Richard F Spaide MD
DORC International, bv/Dutch Ophthalmic, USA: P
Quark Pharmaceuticals: C
Topcon Medical Systems Inc.: C,P

Sunil K Srivastava MD
Allergan: C,S
Bausch + Lomb: C,S
Carl Zeiss Inc.: C
Gilead Sciences: C
Optos Inc.: C
pSivida: C
Regeneron Pharmaceuticals Inc.: C
Santen Inc.: C,S

Paulo E Stanga MD
Allergan: C,L
Bausch Lomb: C,L,S
Bayer Healthcare Pharmaceuticals: C,L
Carl Zeiss Inc: C,L,S
Ellex: C,S
NightstaRx Ltd.: C,S
Novartis Pharmaceuticals Corporation: C
Optos, Inc.: C,L,S
Second Sight Medical Products, Inc.: C,L,S
ThromboGenics Ltd: C,L
Topcon Medical Systems Inc.: C,L,P,S

Giovanni Staurenghi MD
Bayer Healthcare Pharmaceuticals: C
Boheringer: C
Carl Zeiss Meditec: C,S,L
Centervue: C,L,S
GENENTECH: C
Heidelberg Engineering: C,L,S
Hoffman La Roche, Ltd.: C,L,S
Nidek, Inc.: S
Novartis Pharmaceuticals Corporation: C,L,S
Ocular Instruments Inc: P
Optos, Inc.: C
Optovue, Inc.: S
Quantel Medical: C,L,S

Paul Sternberg Jr MD
International Retinal Research Foundation: C,S
Nektar Therapeutics: C

Edwin M Stone MD PhD
None

Jennifer K Sun MD
Adaptive Sensory Technology: S
Boston Micromachines: S
Current Diabetes Reports: E
Genentech: S
JAMA Ophthalmology: E
Kalvista: S
Merck & Co. Inc.: C
Novartis Pharmaceuticals Corp.: C
Optovue: S

Ramin Tadayoni MD PhD
Alcon Laboratories, Inc.: C
Alimera Sciences, Inc.: C
Allergan: C
Bausch + Lomb: C
Bayer Healthcare Pharmaceuticals: C
Carl Zeiss Meditec: C
Chibret International: C
FCI Ophthalmics: C
GENENTECH: C
MORIA: C
Novartis, Alcon Pharmaceuticals: C
Roche Diagnostics: C
ThromboGenics, Inc.: C

Hiroko Terasaki MD
Alcon Laboratories Inc.: C,L,S
Alcon Pharma: L,S
Bayer Healthcare Pharmaceuticals: L,S
Graybug: L
Kowa: S
Novartis: L,S
Otsuka: L,S
Santen Inc.: L,S
Wakamoto: L,S
Zeiss: L

Asheesh Tewari MD
Bausch + Lomb: C,P
Beaver-Visitec International Inc.: C
DORC International, bv/Dutch Ophthalmic, USA: C

John T Thompson MD
Genentech: C,S
Opthea: S
Regeneron Pharmaceuticals Inc.: S

Daniele Tognetto MD
None

Paul E Tornambe MD
Clearside: C,O
Optos Inc.: C,L
Optovue Inc.: L,C
Poway Retinal Technologies: O,P

Cynthia A Toth MD
Alcon Laboratories Inc.: P
EMMES: C

Michael T Trese MD
Digisight: C,O
Interview Medical Systems: O,P
Phoenix Clinical Technologies: C,O
Retinal Solutions: O,P

Russell N Van Gelder MD PhD
Elasmogen: S
National Eye Institute: S

Albert T Vitale MD
AbbVie: C
Aciont: C

Alan L Wagner
Alimera Sciences Inc.: S
Bon Secours Surgery Center: O
Inc Research: S
PPD Investigator Services: O
University of Virginia, Office of Sponsored Programs: S
Vestrum Health: O
Wagner Macula and Retina Center: E

Nadia Khalida Waheed MD
Bayer Healthcare Pharmaceuticals: S
Carl Zeiss Meditec: S
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

Dale Webster PhD
Google: E

John A Wells III MD
Genentech: C,S
Iconic Pharmaceuticals: C
Jaeb Center for Health Research: C,S
KalVista: S
National Eye Institute: S
Ohr Pharmaceuticals: S
Opthea: S
Optos Inc.: S
Regeneron : S

George A Williams MD
OMIC-Ophthalmic Mutual Insurance Company: E

David J Wilson MD
None

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
Roche: S,C

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
Genentech: C,S,L
Novartis Pharma AG: C,L,S
Roche Diagnostics: C,L,S

Lihteh Wu MD
Bayer Health: C,L
Heidelberg Engineering: L
Novartis Pharmaceuticals Corp.: C
Quantel Medical: C,L

Charles C Wykoff MD PhD
Adverum Biotechnologies: S
Aerpio Therapeutics: S
Alcon Laboratories, Inc.: S
Aldeyra Therapeutics: S
Alimera Sciences, Inc.: C
Allegro Ophthalmics: S
Allergan: C,L,S
Alnylam Pharmaceuticals: C
Apellis Pharmaceuticals: S
Astellas Pharma: S
Aura Biosciences, Inc.: S
Bayer Healthcare Pharmaceuticals: C
Boehringer Ingelheim: S
Chiltern International: S
Clearside Biomedical, Inc: C,S
CORCEPT: C
Dutch Ophthalmic Research Center International: C
Evolve Medical Education: C
EyePoint Pharmaceuticals (formerly pSivida): C,S
GENENTECH: C,S
Heidelberg Engineering: S
Iconic Therapeutics: S
inc Research: S
Johns Hopkins University: S
k2c Medical Communications: C
National Eye Institute: S
Notal Vision, Inc.: C
Novartis Pharmaceuticals Corporation: S,C
OHR Pharmaceuticals: S
ONL Therapeutic: C
Ophthotech Corporation: S
Ora, Inc.: S
PRIME Education: C
Regeneron Pharmaceuticals, Inc.: C,L,S
Regenxbio: S
Roche: C,S
Santen, Inc.: C,S
SciFluor Life Sciences, LLC: S
Taiwan Liposome Company: S
Tyrogenex: S

Lawrence A Yannuzzi MD
None

Steven Yeh MD
Clearside: C
Santen Inc.: C

Young Hee Yoon MD
Alcon Laboratories Inc.: C,L
Allergan: C,L,S
Bayer Healthcare Pharmaceuticals: C,L,S
Boeringer Ingelheim: C

Seung Young Yu MD PhD
Allergan Medical Affairs: S
Bayer Healthcare Pharmaceuticals: S
Novartis, Alcon Pharmaceuticals: S
Santen Inc.: S

David N Zacks MD PhD
ONL Therapeutics: C,O,P

Marco A Zarbin MD PhD FACS
Boerhinger Ingelheim Pharma: C
Calhoun Vision, Inc.: C
Cell Cure: C
Chengdu Kanghong Biotechnology Company: C
Coherus Biosciences: C
Daiichi Sankyo: C
EyEngineering: C
Frequency Therapeutics: C,O
GENENTECH: C
Helios, KK: C
Hoffman La Roche, Ltd.: C
IRIDEX: C,L
Isarna Therapeutics: C
Makindus: C
Novartis Pharmaceuticals Corporation: C,L
Ophthotech, Inc.: C
Percept Corp.: C,O
Rutgers University: P

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

Retina Subspecialty Day Exhibits and Break with the Experts

Retina Exhibits

Hall E

Friday, Oct. 26, 9:30 AM - 4:30 PM

Exhibits are not eligible for CME credit.

Break with the Experts

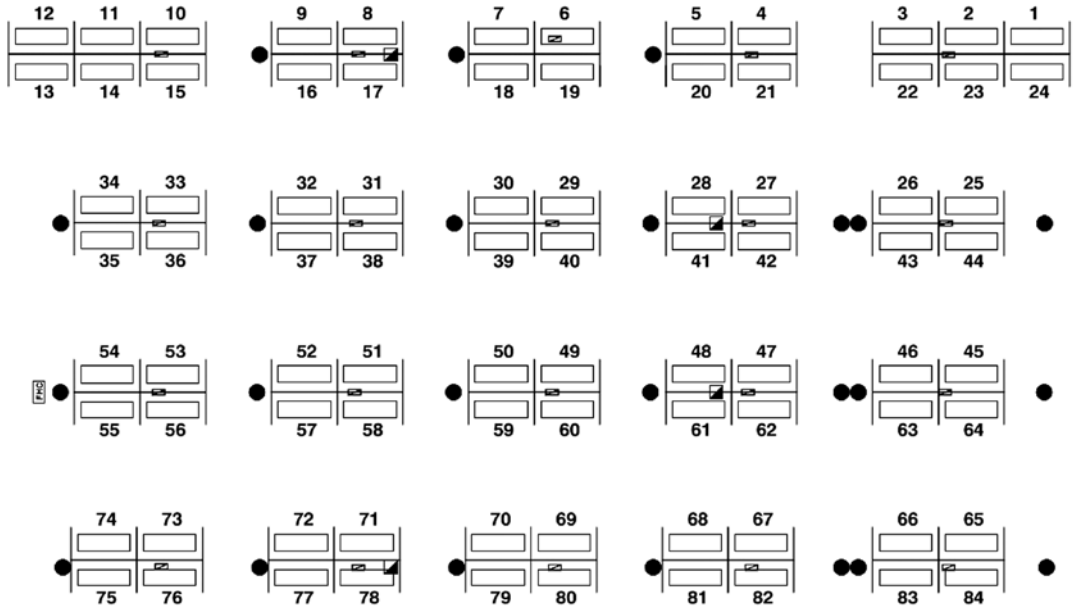
Hall E

Friday, Oct. 26, 3:35 PM - 4:20 PM

Break with the Experts is not eligible for CME credit.

Retina Exhibits

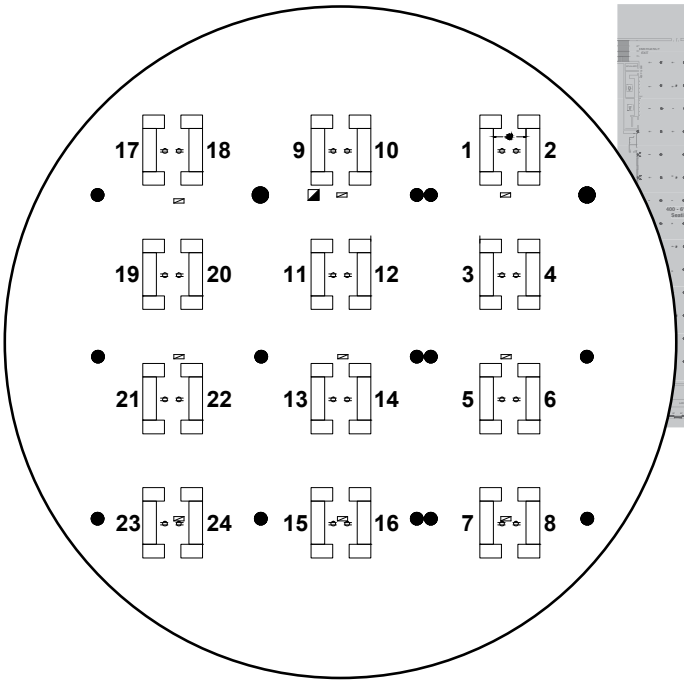
Hall E: Friday, Oct. 26, 9:30 AM – 4:30 PM

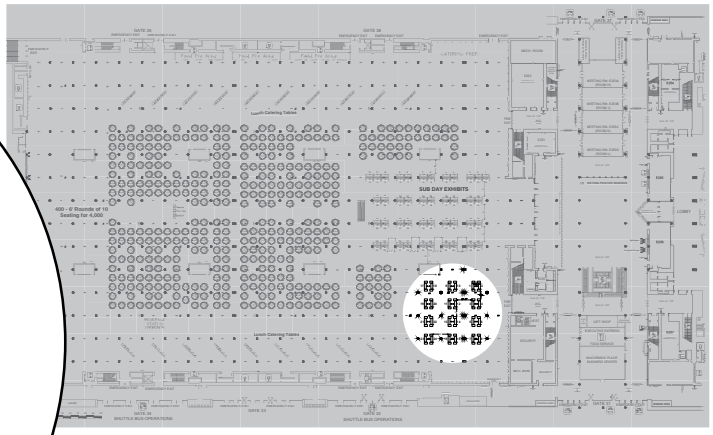


Exhibiting companies with more than one booth have been listed by the lowest booth number.

Retina Subspecialty Day 2018
Hall E — Friday, Oct. 26, 3:35 PM - 4:20 PM
Break with the Experts Schedule & Floor Plan

AAO 2018
ART + SCIENCE
SUBSPECIALTY DAY





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