Retina 2021
Emerging Even Stronger

Program Directors
Mark W Johnson MD and Srinivas R Sadda MD

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

Ernest N Morial Convention Center
New Orleans, Louisiana
Friday – Saturday, Nov. 12 – 13, 2021

Presented by:
The American Academy of Ophthalmology

Supported by an unrestricted educational grant from Genentech

AMERICAN ACADEMY OF OPHTHALMOLOGY®
Protecting Sight. Empowering Lives.

Retina 2021 Planning Group
Mark W Johnson MD
Program Director

Srinivas R Sadda MD
Program Director

Barbara Ann Blodi MD
Timothy G Murray MD MBA

Former Program Directors

2020	Judy E Kim MD Mark W Johnson MD
2019	Mark S Humayan MD PhD Judy E Kim MD
2018	Richard F Spaide MD Mark S Humayan MD PhD
2017	Carl D Regillo MD Richard F Spaide MD
2016	Jennifer I Lim MD Carl D Regillo MD
2015	Pravin U Dugel MD Jennifer I Lim MD
2014	Peter K Kaiser MD Pravin U Dugel MD
2013	Tarek S Hassan MD Peter K Kaiser MD
2012	Joan W Miller MD Tarek S Hassan MD
2011	Allen C Ho MD Joan W Miller MD
2010	Daniel F Martin MD Allen C Ho MD
2009	Antonio Capone Jr MD Daniel F Martin MD
2008	M Gilbert Grand MD Antonio Capone Jr MD
2007	John T Thompson MD M Gilbert Grand MD
2006	Emily Y Chew MD John T Thompson MD
2005	Michael T Trese MD Emily Y Chew MD
2004	William F Mieler MD Michael T Trese MD
2003	Kirk H Packo MD William F Mieler MD
2002	Mark S Blumenkranz MD Kirk H Packo MD
2001	George A Williams MD Mark S Blumenkranz MD
2000	Julia A Haller MD George A Williams MD
1999	Stanley Chang MD Julia A Haller MD
1998	Harry W Flynn Jr MD Stanley Chang MD
1997	H MacKenzie Freeman MD Harry W Flynn Jr MD
1996	H MacKenzie Freeman MD
1995	Thomas M Aaberg Sr MD Paul Sternberg Jr MD

Subspecialty Day Advisory Committee
R Michael Siatkowski MD
Associate Secretary

Bonnie An Henderson MD
Michael S Lee MD
Jennifer Irene Lim MD
Shahzad I Mian MD
Jody R Piltz MD

Maria M Aaron MD
Secretary for Annual Meeting

Staff
Melanie R Rafaty CMP, *Director, Scientific Meetings*
Ann L'Estrange, *Subspecialty Day Manager*
Debra Rosencrance CMP CAE, *Vice President, Meetings & Exhibits*
Patricia Heinicke Jr, *Copy Editor*
Mark Ong, *Designer*
Gina Comaduran, *Cover Design*

2021 Retina Subspecialty Day Planning Group

On behalf of the American Academy of Ophthalmology and the American Society of Retina Specialists, the Macula Society, the Retina Society, and Club Jules Gonin, it is our pleasure to welcome you to New Orleans and **Retina 2021: Emerging Even Stronger.**

Mark W Johnson MD
Program Director

Amgen: C
Apellis: S
Aura Biosciences: C
Pfizer, Inc.: C

Srinivas R Sadda MD
Program Director

4DMT: C | Allergan: C
Amgen: C | Apellis: C
Astellas: C
Bayer Healthcare Pharmaceuticals: C
Carl Zeiss Meditec: C,L,S
Centervue: C | Genentech: C
Heidelberg Engineering: C,L,S
Iveric Bio: C | Merck & Co.: C
Nidek: L
Novartis Pharma AG: C,L
Optos, Inc.: C | Oxurion: C
Regeneron Pharmaceuticals, Inc.: C
Topcon Medical Systems, Inc.: L

Program Planning Group

Barbara Ann Blodi MD
None

Timothy G Murray MD MBA
Alcon Laboratories, Inc.: C
FDA: C

2021 Subspecialty Day Advisory Committee

R Michael Siatkowski MD, Chair (Pediatric Ophthalmology)
National Eye Institute: S
OMIC-Ophthalmic Mutual Insurance Company: C

Maria M Aaron MD (Secretary for Annual Meeting)
None

Bonnie An Henderson MD (Refractive Surgery)
Alcon Laboratories, Inc.: C,L

Michael S Lee MD (Neuro-Ophthalmology)
Horizon: O
Springer: P
Sun Biopharma: C
UpToDate: P

Jennifer Irene Lim MD (Retina)
Aldeyra Therapeutics: S
Allergan, Inc.: C
Aura Biosciences: C
Chengdu Kanghong: S
Cognition Therapeutics: C
CRC Press/Taylor and Francis: P
Eyenuk: C
Genentech: C,S
Greybug: S
Iveric Bio: C
JAMA Ophthalmology Editorial Board: C
Luxa: C
NGM: S
Novartis Pharma AG: C
Ophthea: C
Quark: C
Regeneron Pharmaceuticals, Inc.: S,C
Santen, Inc.: C
Stealth: S
Unity: C
Viridian: C

Shahzad I Mian MD (Cornea)
Centrasight: S
Kowa American Corporation: S
National Eye Institute: S

Jody R Piltz MD (Glaucoma)
Aerie Pharmaceuticals: C,L,S

AAO Staff

Ann L'Estrange
None

Melanie Rafaty
None

Debra Rosencrance
None

Beth Wilson
None

Retina 2021 Contents

CME Credit

The Academy's CME Mission Statement

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

2021 Retina Subspecialty Day Meeting Learning Objectives

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

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

2021 Retina Subspecialty Day Meeting Target Audience

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

Teaching at a Live Activity

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

Scientific Integrity and Disclosure of Conflicts of Interest

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

Control of Content

The Academy 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.

2021 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.

Friday Subspecialty Day Activity: Glaucoma, Neuro-Ophthalmology, Pediatric Ophthalmology, Refractive Surgery, and Retina (Day 1)

The Academy designates this Other (blended live and enduring material) activity for a maximum of *12 AMA PRA Category 1 Credits*™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

Saturday Subspecialty Day Activity: Cornea, Oculofacial Plastic Surgery, and Retina (Day 2)

The Academy designates this Other (blended live and enduring material) activity for a maximum of *12 AMA PRA Category 1 Credits*™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

Physicians registered as In Person and Virtual are eligible to claim the above CME credit.

How to Claim CME

Attendees can claim credits online.

For AAO 2021, you can claim CME credit multiple times, up to the 50-credit maximum, through Aug. 1, 2022. You can claim some in 2021 and some in 2022, or all in the same year.

For 2021 Subspecialty Day, you can claim CME credit multiple times, up to the 12-credit maximum per day, through Aug. 1, 2022. You can claim some in 2021 and some in 2022, or all in the same year.

You do not need to track which sessions you attend, just the total number of hours you spend in sessions for each claim.

Academy Members

CME transcripts that include AAOE Half-Day Coding Sessions, Subspecialty Day and/or AAO 2021 credits will be available to Academy members through the Academy's CME Central web page.

The Academy transcript cannot list individual course attendance. It will list only the overall credits claimed for educational activities at AAOE Half-Day Coding Sessions, Subspecialty Day and/or AAO 2021.

Nonmembers

The Academy provides nonmembers with verification of credits earned and reported for a single Academy-sponsored CME activity.

Proof of Attendance

You will be able to obtain a CME credit reporting/ proof-of-attendance letter for reimbursement or hospital privileges, or for nonmembers who need it to report CME credit:

Academy Members

When you claim CME credits and complete the evaluation, you will be able to print a certificate/proof of attendance letter from your transcript page. Your certificate will also be emailed to you.

Nonmembers

When you claim CME credits and complete the evaluation, a new browser window will open with a PDF of your certificate. Please disable your pop-up blocker. Your certificate will also be emailed to you.

CME Questions

Send your questions about CME credit reporting to cme@aao.org.

For Continuing Certification questions, contact the American Board of Ophthalmology at MOC@abpo.org.

The Charles L Schepens MD Lecture

Advanced Retinal Implants

Mark S Humayun MD PhD

FRIDAY, NOV. 12, 2021

9:57 AM – 10:17 AM

Mark S Humayun MD PhD

Mark S Humayun MD PhD is the Cornelius J Pings Chair in Biomedical Sciences; Professor of Ophthalmology, Biomedical Engineering, and Integrative Anatomical Sciences; Director of the USC Ginsburg Institute for Biomedical Therapeutics; and Codirector of the USC Roski Eye Institute.

Dr. Humayun is an internationally recognized pioneer in vision restoration. He assembled a team of multidisciplinary experts to develop the first FDA-approved artificial retina, Argus II, for sight restoration. He has more than 125 issued patents and over 250 peer-reviewed publications. He has a Google Scholar h-index of 90. Dr. Humayun is a member of the U.S. National Academies of Medicine, Engineering, and Inventors. He was named in the top 1% of ophthalmologists by the *U.S. News & World Report*. For his extraordinary contributions he was awarded the United States' highest technological achievement, the 2015 National Medal of Technology and Innovation, by President Obama. He is an IEEE Fellow and the recipient of the 2018 IEEE Biomedical Engineering Award and the 2020 IEEE Medal for Innovations in Healthcare Technology.

Faculty

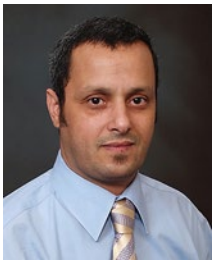
David H Abramson MD FACS
New York, NY

Robert L Avery MD
Santa Barbara, CA

Caroline R Baumal MD
Boston, MA

Nisha Acharya MD
San Francisco, CA

Marcos P Avila MD
Goiania, GO, Brazil



Lbachir Benmohamed PhD
Irvine, CA

Anita Agarwal MD
San Francisco, CA

Carl C Awh MD
Nashville, TN

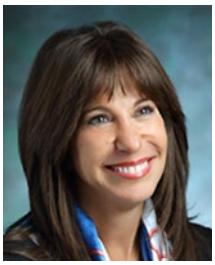
Audina M Berrocal MD
Miami, FL

Lloyd P Aiello MD PhD
Boston, MA

Sophie J Bakri MD
Rochester, MN

Maria H Berrocal MD
San Juan, PR

Cagri G Besirli MD
Ann Arbor, MI



Susan B Bressler MD
Baltimore, MD

Usha Chakravarthy MBBS PhD
Belfast, Northern Ireland

Barbara Ann Blodi MD
Madison, WI

David M Brown MD
Houston, TX

R V Paul Chan MD
Chicago, IL

David S Boyer MD
Los Angeles, CA

Peter A Campochiaro MD
Baltimore, MD

Jonathan Chang MD
Madison, WI

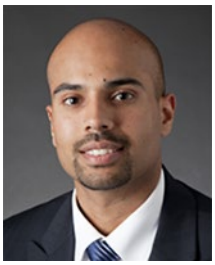
Neil M Bressler MD
Baltimore, MD

Antonio Capone Jr MD
Royal Oak, MI

Stanley Chang MD
New York, NY

Steven T Charles MD
Germantown, TN

David R Chow MD
North York, ON, Canada



Dilsher S Dhoot MD
Valencia, CA

Emily Y Chew MD
Bethesda, MD

Karl G Csaky MD
Dallas, TX

Diana V Do MD
Los Altos, CA

Michael F Chiang MD
Bethesda, MD

Donald J D'Amico MD
New York, NY

Jay S Duker MD
Boston, MA

No photo available

Netan Choudhry MD
Etobicoke, ON, Canada

No photo available

Vaidehi Shradha Dedania MD
New York, NY

Jacque L Duncan MD
San Francisco, CA

Justis P Ehlers MD
Shaker Heights, OH

Nicole Eter MD
Muenster, Germany

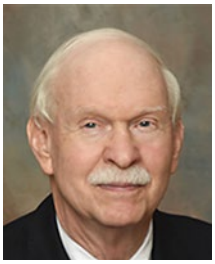
K Bailey Freund MD
New York, NY

David A Eichenbaum MD
St Petersburg, FL

Amani Fawzi MD
Chicago, IL

Gerardo Garcia-Aguirre MD
Mexico City, DF, Mexico

Dean Eliott MD
Boston, MA



Harry W Flynn Jr MD
Miami, FL

Sunir J Garg MD FACS
Gladwyne, PA

Geoffrey G Emerson MD PhD
Minneapolis, MN

Jasmine H Francis MD
New York, NY

Alain Gaudric MD
Paris, France

Mark C Gillies MD PhD
Sydney, NSW, Australia

Dilraj Singh Grewal MD
Durham, NC

J William Harbour MD
Miami, FL

Roger A Goldberg MD
Walnut Creek, CA

Robyn H Guymer MBBS PhD
East Melbourne, VIC, Australia

Tarek S Hassan MD
Royal Oak, MI

Justin Gottlieb MD
Madison, WI

Paul Hahn MD PhD
Tenafly, NJ

Jeffrey S Heier MD
Boston, MA

Evangelos S Gragoudas MD
Boston, MA

Julia A Haller MD
Philadelphia, PA

Allen C Ho MD
Philadelphia, PA

Suber S Huang MD MBA
Cleveland, OH

Deeba Husain MD
Boston, MA

Lee M Jampol MD
Chicago, IL

G Baker Hubbard MD
Atlanta, GA

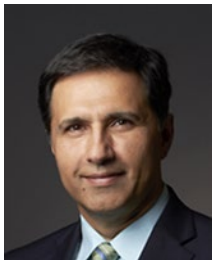
Michael S Ip MD
Pasadena, CA

Kanishka T Jayasundera MD
Ann Arbor, MI

Jean-Pierre Hubschman MD
Los Angeles, CA

Douglas A Jabs MD MBA
Baltimore, MD

Mark W Johnson MD
Ann Arbor, MI



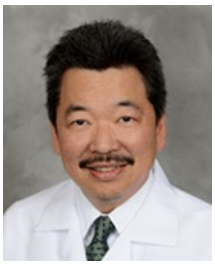
Mark S Humayun MD PhD
Los Angeles, CA

Glenn J Jaffe MD
Durham, NC

J Michael Jumper MD
San Francisco, CA

Peter K Kaiser MD
Cleveland, OH

Ivana K Kim MD
Boston, MA



Gregg T Kokame MD
Aiea, HI

Richard S Kaiser MD
Philadelphia, PA

Judy E Kim MD
Milwaukee, WI

Baruch D Kuppermann MD PhD
Irvine, CA

Pearse A Keane MBBCh
London, United Kingdom

Stephen J Kim MD
Nashville, TN

Eleonora G Lad MD PhD
Durham, NC

Arshad M Khanani MD
Reno, NV

Shoji Kishi MD PhD
Maebashi, Gunma, Japan

No photo available

David R Lally MD
Avon, CT

Aaron Y Lee MD
Mercer Island, WA

Phoebe Lin MD PhD
Portland, OR

Raj K Maturi MD
Indianapolis, IN

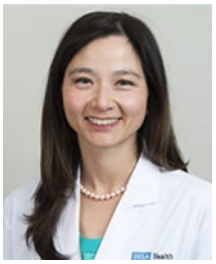
Gareth M Lema MD PhD
New York, NY

Anat Loewenstein MD
Tel Aviv, Israel

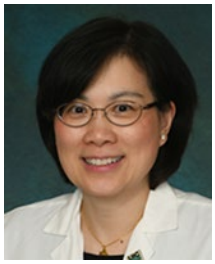
Colin A McCannel MD
Los Angeles, CA

Theodore Leng MD
Palo Alto, CA

Mathew W MacCumber MD PhD
Chicago, IL



Tara A McCannel MD
Los Angeles, CA



Jennifer Irene Lim MD
Chicago, IL

Daniel F Martin MD
Cleveland, OH

H Richard McDonald MD
San Francisco, CA

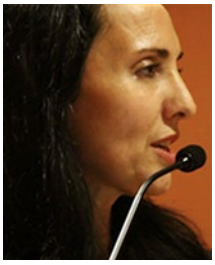
Carsten H Meyer MD
Davos, Switzerland

Quan Dong Nguyen MD
Palo Alto, CA

David W Parke II MD
San Francisco, CA

William F Mieler MD
Winnetka, IL

Kyoko Ohno-Matsui MD
Tokyo, Japan



Barbara Parolini MD
Brescia, BS, Italy

Prithvi Mruthyunjaya MD
Palo Alto, CA

Timothy W Olsen MD
Rochester, MN

Grazia Pertile MD
Negrar, VR, Italy

Timothy G Murray MD MBA
South Miami, FL

Susanna S Park MD PhD
Sacramento, CA

Dante Pieramici MD
Santa Barbara, CA

John S Pollack MD
Joliet, IL

Carl D Regillo MD FACS
Bryn Mawr, PA

Srinivas R Sadda MD
Los Angeles, CA

Jonathan L Prenner MD
Princeton, NJ

Kourous Rezaei MD
Harvey, IL

Jose A Sahel MD
Pittsburgh, PA

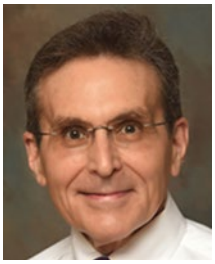
No photo available

Firas M Rahhal MD
Beverly Hills, CA

Richard B Rosen MD
New York, NY

David Sarraf MD
Los Angeles, CA

Rajesh C Rao MD
Ann Arbor, MI



Philip J Rosenfeld MD PhD
Miami, FL

Shlomit Schaal MD PhD
Worcester, MA

Ursula M Schmidt-Erfurth MD
Vienna, Austria

Gaurav K Shah MD
Saint Louis, MO

Lawrence J Singerman MD
Beachwood, OH

No photo available

Steven D Schwartz MD
Los Angeles, CA

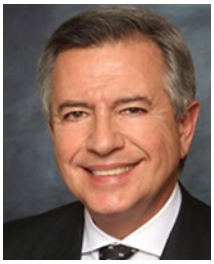
Veeral Sheth MD
Hinsdale, IL

Rishi P Singh MD
Cleveland, OH

Adrienne Williams Scott MD
Baltimore, MD

Paul A Sieving MD PhD
Sacramento, CA

Elliott H Sohn MD
Iowa City, IA



J Sebag MD FACS FRCOphth FARVO
Huntington Beach, CA

Michael A Singer MD
San Antonio, TX

Sharon D Solomon MD
Baltimore, MD

Richard F Spaide MD
New York, NY

Giovanni Staurenghi MD
Milan, Italy

John T Thompson MD
Baltimore, MD

Sunil K Srivastava MD
Cleveland, OH

Paul Sternberg Jr MD
Nashville, TN

Nadia Khalida Waheed MD
West Roxbury, MA

Peter W Stalmans MD PhD
Leuven, Belgium

Jennifer K Sun MD
Boston, MA

John A Wells III MD
West Columbia, SC

No photo available

Paulo E Stanga MD
London, United Kingdom

Ramin Tadayoni MD PhD
Paris, France

Christina Y Weng MD MBA
Houston, TX

George A Williams MD
Royal Oak, MI

Charles C Wykoff MD PhD
Bellaire, TX

No photo available

David N Zacks MD PhD
Ann Arbor, MI

Sebastian Wolf MD PhD
Bern, Switzerland

Glenn C Yiu MD PhD
Sacramento, CA

Marco A Zarbin MD PhD FACS
Chatham, NJ

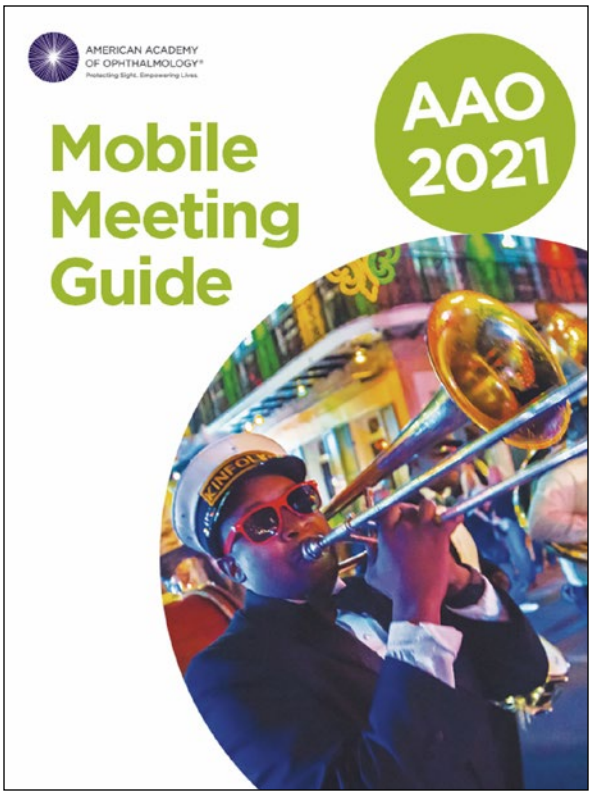
Tien Yin Wong MBBS
Singapore, Singapore

Yoshihiro Yonekawa MD
Bryn Mawr, PA

Respond to Polls Live During the Meeting Using the Mobile Meeting Guide

To submit an answer to a poll or ask the moderator a question during the meeting, follow the directions below.

- Access at www.aao.org/mobile
- Select "Program," "Handouts & Evals"
- Filter by meeting: Retina Meeting
- Select "Current Session"
- Select "Interact with this session (live)" link to open a new window
- Choose "Answer Poll"



Retina 2021: Emerging Even Stronger

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

FRIDAY, NOV. 12, 2021

7:00 AM	CONTINENTAL BREAKFAST		
8:00 AM	Welcome and Introductions	Mark W Johnson MD* Srinivas R Sadda MD*	
Section I:	**Vitreoretinal Surgery, Part I**		
	Moderator: Steven T Charles MD*		
	Morning Sessions Virtual Moderator: Adrienne Williams Scott MD		
8:03 AM	Advances in Complex Ocular Construction in Association With Permanent Boston Keratoprosthesis Placement	Donald J D'Amico MD*	1
8:09 AM	Management of Fellow Eyes of Patients With Nontraumatic Giant Retinal Tears	Harry W Flynn Jr MD	4
8:15 AM	Tips for Handling Complex Retinal Detachments	Dean Eliott MD*	7
8:21 AM	Management of Vision-Obscuring Vitreous Hemorrhage Associated With Posterior Vitreous Detachment: Observe or Operate?	Gaurav K Shah MD*	10
8:27 AM	Vitrectomy for Diabetic Traction Retinoschisis	Stanley Chang MD*	11
8:33 AM	Submacular Hemorrhage: Surgical Indications and Technique	Sophie J Bakri MD*	12
8:39 AM	Giant Internal Limiting Membrane Tears: Pathogenesis, Clinical Characteristics, and Surgical Utility	Mark W Johnson MD*	13
8:45 AM	New Strategies to Treat Myopic, Chronic, and Persistent Macular Holes	John T Thompson MD*	15
8:51 AM	Vitreoretinal Surgery Panel Panel Moderator: H Richard McDonald MD Panelists: Sophie J Bakri MD*, Jonathan Chang MD, Dean Eliott MD* and John T Thompson MD*		17
Section II:	**Public Health, Education, and the Business of Retina**		
	Moderator: George A Williams MD		
9:06 AM	A Multicountry Analysis of the Effect of COVID-19 on Outcomes of VEGF Inhibitor Therapy	Mark C Gillies MD PhD*	18
9:12 AM	Developing a Pancoronavirus Vaccine	Lbachir Benmohamed PhD	19
9:18 AM	What the Retina Specialist Should Know About Activities at the National Eye Institute	Michael F Chiang MD*	20
9:24 AM	Current Status of U.S. Fellowship Monitoring and Compliance	Justin Gottlieb MD	21
9:30 AM	The Process of Quality	Timothy W Olsen MD*	22
9:36 AM	Diversity, Equity, and Inclusion in Retina	Julia A Haller MD*	23
9:42 AM	Variations in Vitreoretinal Physician Utilization of Ancillary Testing: An IRIS® Registry Analysis	Theodore Leng MD*	26
9:47 AM	In These Unprecedented Times . . .	Gareth M Lema MD PhD	27

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

The Charles L Schepens MD Lecture

9:52 AM	Introduction of the 2021 Charles L Schepens MD Lecturer	David W Parke II MD*	
9:57 AM	The Charles L Schepens MD Lecture: Advanced Retinal Implants	Mark S Humayun MD PhD*	29
10:17 AM	REFRESHMENT BREAK		

Section III: My Best Medical Retina Case

Moderator: William F Mieler MD

10:57 AM	Case Presentation	William F Mieler MD	30
11:00 AM	Discussion		
11:03 AM	Case Presentation	David Sarraf MD*	30
11:06 AM	Discussion		
11:09 AM	Case Presentation	J Michael Jumper MD*	30
11:12 AM	Discussion		
11:15 AM	Case Presentation	Amani Fawzi MD*	30
11:18 AM	Discussion		
11:21 AM	Case Presentation	Lee M Jampol MD*	30
11:24 AM	Discussion		

Section IV: Medical Retina and Chorioretinal Vascular Disease

Moderator: Anita Agarwal MD

11:27 AM	Should We Reconsider the Diagnosis of Idiopathic Uveal Effusion Syndrome?	Alain Gaudric MD	31
11:33 AM	Central Serous Choroidopathy: What Can We Learn From OCT Angiography?	Nicole Eter MD*	33
11:39 AM	Patterns of Choroidal Venous Insufficiency Influencing Pachychoroid Disease	K Bailey Freund MD*	34
11:45 AM	Beyond Pachychoroid: Venous Overload Chorioretinopathy	Richard F Spaide MD*	35
11:51 AM	How Does the Venous Outflow Pathway Change in Central Serous Chorioretinopathy?	Shoji Kishi MD PhD	36
11:57 AM	What's New in Retinal Dystrophies?	Jacque L Duncan MD*	40
12:03 PM	Blood–Brain Barrier Disruption Maculopathy	Phoebe Lin MD PhD	42
12:09 PM	The Role of the Intestinal Microbiome in Retinal Diseases	Sebastian Wolf MD PhD*	43
12:15 PM	LUNCH		

Section V: Uveitis

Moderator: Sunil K Srivastava MD*

Afternoon Sessions Virtual Moderator: Vaidehi Shradha Dedania MD

1:40 PM	Update on Uveitic Macular Edema	Douglas A Jabs MD MBA	44
1:46 PM	Update on Intraocular Sustained Drug Delivery for Uveitis	Glenn J Jaffe MD*	45
1:52 PM	Novel Therapies in Development for Noninfectious Intermediate, Posterior, and Pan-Uveitis	Quan Dong Nguyen MD*	46

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

1:58 PM	Uveitis Panel Discussion Panel Moderator: Sunil K Srivastava MD* Panelists: Nisha Acharya MD, Stephen J Kim MD, Phoebe Lin MD PhD		47

Section VI: The 2021 Debates

Moderators: Tarek S Hassan MD* and John S Pollack MD*

2:13 PM	Telemedicine Screening for Diabetic Retinopathy Is Ready to Go	Jennifer Irene Lim MD*	48
2:16 PM	Telemedicine Screening for Diabetic Retinopathy Has a Ways to Go	Christina Y Weng MD MBA*	50
2:19 PM	Audience Vote		
2:20 PM	The Risk/Benefit Ratio for Brolicizumab Is Acceptable	Rishi P Singh MD*	51
2:23 PM	The Risk/Benefit Ratio for Brolicizumab Is Not Acceptable	Paul Hahn MD PhD*	52
2:26 PM	Audience Vote		
2:27 PM	The Best Treatment for Severe Nonproliferative Diabetic Retinopathy Without Diabetic Macular Edema Is Regular Anti-VEGF Therapy	Diana V Do MD*	53
2:30 PM	The Best Treatment for Severe Nonproliferative Diabetic Retinopathy Without Diabetic Macular Edema Is Regular Observation	Ramin Tadayoni MD PhD*	54
2:33 PM	Audience Vote		
2:34 PM	The Best Procedure for Large Refractory Macular Hole Is Autologous Retinal Transplantation	Dilraj Singh Grewal MD*	56
2:37 PM	The Best Procedure for Large Refractory Macular Hole Is Perifoveal Hydrodissection	Carsten H Meyer MD	57
2:40 PM	Audience Vote		

Section VII: Late Breaking Developments, Part I

Moderator: Mark S Humayun MD PhD*

Panelists: Kanishka T Jayasundera MD, Dante Pieramici MD*, Shlomit Schaal MD PhD, and Elliott H Sohn MD*

2:41 PM	Brolucizumab for Treatment of Diabetic Macular Edema (DME): 52-Week Results From the KESTREL and KITE Phase 3 Studies	Dilsher S Dhoot MD*	60
2:46 PM	A Treatment-Agnostic Analysis of the Long-Term Impact of IRF and SRF on Vision and Anatomy in nAMD in the HAWK and HARRIER Studies	David A Eichenbaum MD*	60
2:51 PM	Discussion		
2:56 PM	Dosing Errors With Aflibercept Pre-filled Syringe	Roger A Goldberg MD*	60
3:01 PM	New Navigated Single-Capture 3D and Cross-Sectional Wide-Field OCT of the Mid and Peripheral Retina and Vitreoretinal Interface	Paulo E Stanga MD*	60
3:06 PM	Discussion		
3:11 PM	Optogenetics in the Clinic: Safety and Efficacy Updates on the Phase I/II Clinical Trial PIONEER	Jose A Sahel MD*	60
3:16 PM	Long-term Evaluation of Retinitis Pigmentosa (RP) Patients Implanted with a Novel Epiretinal Prosthetic Device	Peter W Stalmans MD PhD*	60
3:21 PM	Discussion		

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

Section VIII:	**First-time Results of Clinical Trials**		
	Moderator: Deeba Husain MD*		
3:26 PM	Results From a Phase 2 Study of ADVM-022 Intravitreal Gene Therapy for Diabetic Macula Edema: The INFINITY Trial	David S Boyer MD*	61
3:32 PM	Two-Year Results From the Subretinal RGX-314 Gene Therapy Phase 1/2a Study for the Treatment of nAMD and an Update on Suprachoroidal Trials	Robert L Avery MD*	64
3:38 PM	Treatment of Geographic Atrophy Secondary to AMD With Pegcetacoplan: Updates on the Randomized Phase 3 DERBY and OAKS Trials	Charles C Wykoff MD PhD*	66
3:44 PM	MERLIN: Results From the Phase 3a Trial of Brolucizumab in Patients With nAMD and Resistant Retinal Fluid	Arshad M Khanani MD*	67
3:50 PM	Three-Year Results of the PALADIN Study of the Fluocinolone Implant for Diabetic Macular Edema	Michael A Singer MD*	68
3:56 PM	Closing Remarks	Mark W Johnson MD* Srinivas R Sadda MD*	

SATURDAY, NOV. 13, 2021

8:00 AM	Opening Remarks	Mark W Johnson MD* Srinivas R Sadda MD*	

Section IX:	**Imaging**		
	Moderator: Steven D Schwartz MD*		
	Morning Sessions Virtual Moderator: Richard S Kaiser MD		
8:05 AM	Novel OCT Findings	Caroline R Baumal MD*	69
8:11 AM	OCT Imaging of the Retinal Periphery	Netan Choudry MD*	71
8:17 AM	Macrophages Swarming the Macula: Visualizing Cellular Activities in Retinal Vascular Disease Using Clinical OCT Images	Richard B Rosen MD*	72
8:23 AM	Visualization of Posterior Vitreous by Ultrawide-field and AI-Based 3-D OCT Imaging	Kyoko Ohno-Matsui MD*	74
8:29 AM	How to Determine Posterior Vitreous Detachment Status With a 10-Second Retinal Nerve Fiber Layer Scan and Patient Age*	David M Brown MD*	77
8:35 AM	OCT Imaging with Optical Attenuation Coefficients	Philip J Rosenfeld MD PhD*	89
8:41 AM	OCT Angiography Update	Nadia Khalida Waheed MD*	92
8:47 AM	Imaging Panel Discussion: OCT Diagnoses You Don't Want to Miss Panel Moderator: Jay S Duker MD* Panelists: Barbara Ann Blodi MD, Justis P Ehlers MD*, Eleonora G Lad MD PhD*, and Nadia Khalida Waheed MD*		93

Section X:	**Late Breaking Developments, Part II**		
	Moderator: Anat Loewenstein MD*		
	Panelists: Colin A McCannel MD*, Srinivas R Sadda MD*, and Paul Sternberg Jr MD*		
9:02 AM	Intravitreal Sunitinib Malate Depot (GB-102): Durability and Safety in Wet Age-Related Macular Degeneration (ALTISSIMO, Phase 2B)	Veeral Sheth MD*	94

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

9:07 AM	Results of a Phase 1 Dose Escalation Open Label Trial Of EYP-1901 in Previously Treated Wet AMD Patients	David S Boyer MD*	94
9:12 AM	Discussion		
9:17 AM	Safety and Efficacy Results of ONS-5010, an Ophthalmic Bevacizumab, From Phase 3 Study of Monthly Intravitreal ONS-5010 in Subjects With Wet AMD (NORSE 2)	Firas M Rahhal MD*	94
9:22 AM	Nascent GA and Intermediate AMD Progression in the GATHER1 Clinical Trial: Post Hoc Analyses of 18-Month Data	David Lally MD*	94
9:27 AM	Discussion		

Section XI: Neovascular AMD

Moderator: Mark W Johnson MD*

9:32 AM	Unanswered Questions in AMD: Trials We Didn't Do in the DRCR Retina Network	Daniel F Martin MD	95
9:38 AM	Port Delivery System Long-term Follow-up	Peter A Campochiaro MD*	96
9:44 AM	Faricimab in Neovascular AMD: One-Year Efficacy, Safety, and Durability in the Phase 3 TENAYA and LUCERNE Trials	Carl D Regillo MD FACS*	98
9:50 AM	Recalcitrant Fluid in Neovascular AMD: Why Does It Not Go Away?	David Sarraf MD*	100
9:56 AM	What's Wrong With Step Therapy for Wet AMD?	Paul Sternberg Jr MD*	101
10:02 AM	Neovascular AMD Panel Discussion Panel Moderator: Sunir J Garg MD FACS* Panelists: Karl G Csaky MD*, Jean-Pierre Hubschman MD*, and Mathew W MacCumber MD PhD*, and Daniel F Martin MD		102
10:17 AM	REFRESHMENT BREAK and AAO 2021 EXHIBITS		

Section XII: Oncology

Moderator: Evangelos S Gragoudas MD*

10:57 AM	Clinically Actionable Mutations in 1700 Patients From the Collaborative Ocular Oncology Group Using a Uveal Melanoma Next-Generation Sequencing Panel	J William Harbour MD*	103
11:03 AM	Retinal Toxicity of Novel Cancer Treatments	Jasmine H Francis MD	105
11:09 AM	Oncology Panel Discussion Panel Moderator: Timothy G Murray MD MBA* Panelists: Jasmine H Francis MD, Ivana K Kim MD*, Tara A McCannel MD, and Prithvi Mruthyunjaya MD*		107

Section XIII: Diabetic Retinopathy

Moderators: Lloyd P Aiello MD PhD* and Jennifer K Sun MD*

11:24 AM	Guidelines for Managing Diabetic Macular Edema Based on Visual Acuity	Neil M Bressler MD*	108
11:30 AM	Faricimab Diabetic Macular Edema Phase 3 Trials	Jeffrey S Heier MD*	110
11:36 AM	Let There Be Light! Photobiomodulation for Diabetic Macular Edema	Judy E Kim MD*	112
11:42 AM	Use of Ultrawide-field Fluorescein Angiography in the Management of Diabetic Retinopathy	Barbara Ann Blodi MD	115
11:48 AM	Lapses in Care When Treating Proliferative Diabetic Retinopathy: What Have We Learned?	Susan B Bressler MD*	116

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

11:54 AM	Panretinal Photocoagulation: A Rational Guide for Its Use	David N Zacks MD PhD*	118
12:00 PM	DRCR Protocol W: Prophylactic Use of Anti-VEGF Treatment	Raj K Maturi MD*	119
12:06 PM	Diabetes Panel Discussion Panel Moderator: Jennifer K Sun MD* Panelists: Lloyd P Aiello MD PhD*, Gregg T Kokame MD*, Susanna S Park MD PhD*, and John A Wells III MD*		121
12:21 PM	LUNCH and AAO 2021 EXHIBITS		

Section XIV: Pediatric Retina

Moderator: G Baker Hubbard MD*

Afternoon Sessions Virtual Moderator: Sharon D Solomon MD

1:41 PM	Update on the International Classification of ROP, 3rd Edition (ICROP3)	R V Paul Chan MD*	122
1:47 PM	Emerging Therapies for Pediatric Retinal Diseases	Antonio Capone Jr MD*	123
1:53 PM	Disparities in Geographic Access to U.S. ROP Treatment Centers	Yoshihiro Yonekawa MD*	124
1:59 PM	Pediatric Retina Panel Discussion Panel Moderator: G Baker Hubbard MD* Panelists: Audina M Berrocal MD*, Cagri G Besirli MD*, R V Paul Chan MD*, and Yoshihiro Yonekawa MD*		126

Section XV: Gene and Cell-Based Therapies

Moderator: Paul A Sieving MD*

2:14 PM	Where Do We Stand With Cell-Based Therapy for Retinal Diseases?	Rajesh C Rao MD*	127
2:20 PM	Delivery Strategies for Gene and Cell Therapies in Retinal Disease	Allen C Ho MD*	128
2:26 PM	Drug and Gene Delivery Through the Suprachoroidal Space	Glenn C Yiu MD PhD*	132
2:32 PM	Real-World Outcomes of Voretigene Neparvovec (Luxturna) Subretinal Gene Therapy	Cagri G Besirli MD*	133
2:38 PM	OpRegen Trial: Phase 1/2a Dose Escalation Study of Human Embryonic Stem Cell–Derived Retinal Pigment Epithelium Cells Transplanted Subretinally in Patients With Advanced AMD	Michael S Ip MD*	135
2:44 PM	Intravitreal Human Retinal Progenitor Cells for the Treatment of Retinitis Pigmentosa	Baruch D Kuppermann MD PhD*	137

Section XVI: Nonexudative AMD

Moderator: Lawrence J Singerman MD*

2:50 PM	OCT Risk Factors for Late AMD: Implications for Clinical Practice	Srinivas R Sadda MD*	139
2:56 PM	Morphologic Features at Conversion From Nonexudative to Exudative AMD	Usha Chakravarthy MBBS PhD*	141
3:02 PM	Ten-Year Follow-up Data From the AREDS2 Study	Emily Y Chew MD	142
3:08 PM	Nascent Geographic Atrophy	Robyn H Guymer MBBS PhD*	143
3:14 PM	Is All Macular Atrophy the Same?	Giovanni Staurenghi MD*	144
3:20 PM	Approaches to Treat Dry AMD in Clinical Trials	Peter K Kaiser MD*	
3:26 PM	REFRESHMENT BREAK and AAO 2021 EXHIBITS		

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

Section XVII: Artificial Intelligence

Moderator: Suber S Huang MD MBA*

4:00 PM	Multicenter, Head-to-Head, Real-World Validation Study of 7 Automated AI Diabetic Retinopathy Screening Systems	Aaron Y Lee MD*	145
4:06 PM	Prediction of Systemic Diseases From Eye Images Using AI and Deep Learning	Tien Yin Wong MBBS*	146
4:12 PM	AI-Based Fluid Monitoring in the Clinical Practice	Ursula M Schmidt-Erfurth MD*	148
4:18 PM	Clinician-Driven Machine Learning: A New Phase for AI-Enabled Health Care?	Pearse A Keane MBBCh*	153

Section XVIII: Vitreoretinal Surgery, Part II

Moderator: Carl C Awh MD*

4:24 PM	New Instrumentation for Vitreoretinal Surgery	David R Chow MD*	154
4:30 PM	Vision-Degrading Myodesopsia	J Sebag MD FACS FRCOphth FARVO*	155
4:36 PM	Management of Myopic Traction Maculopathy	Barbara Parolini MD	156
4:42 PM	Surgical Techniques for Secondary IOLs	Jonathan L Prenner MD*	161
4:48 PM	Rho Kinase Inhibition Reduces Photoreceptor Damage After Retinal Detachment: Possible Implications for Gene and Cell Therapy	Marco A Zarbin MD PhD FACS*	162

Section XIX: Surgical Videos: Cool Cases and Complications

Moderator: Kourous Rezaei MD*

4:54 PM	Subretinal Blu	Grazia Pertile MD	164
4:57 PM	Discussion		
5:00 PM	Suprachoroidal Air	Marcos P Avila MD	164
5:03 PM	Discussion		
5:06 PM	Endophthalmitis	Geoffrey G Emerson MD PhD*	164
5:09 PM	Discussion		
5:12 PM	Endolaser	Gerardo Garcia-Aguirre MD*	164
5:15 PM	Discussion		
5:18 PM	Scleral Buckling and Subretinal Hemorrhage	Maria H Berrocal MD*	164
5:21 PM	Discussion		
5:24 PM	Closing Remarks	Mark W Johnson MD* Srinivas R Sadda MD*	
	ADJOURN		

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

Advances in Complex Ocular Construction in Association With Permanent Boston Keratoprosthesis Placement

Donald J D'Amico MD, Kimberly C Sippel MD, and Szilárd Kiss MD

Introduction

Although the concept of replacing a damaged cornea with a clear artificial device is among the most conceptually straightforward of all surgical goals, many decades of painstaking work have been required to bring this surgery into the mainstream. This presentation will feature the Boston ("Dohlman") Permanent Keratoprosthesis (KPro), which consists of an optically customizable front-plate with stem, an annulus of donor cornea for suturing, and a backplate with locking ring in a sandwich design. A modified version of the device with an additional nub on the front-plate is available for translid placement but is rarely used in our center. Comprehensive reviews regarding the current indications, visual results, and complications are available.[1-4] This presentation will highlight current vitreoretinal aspects related to this complex ocular reconstructive surgery.

Current Practices

At Weill Cornell Ophthalmology, we routinely prefer aphakic KPros and will typically remove the native lens or a pre-exiting IOL with associated capsular debris across the open sky early in the procedure. Our rationale for this includes decreasing chronic inflammatory burden from residual lens material and for ease of access to the posterior surface of the device if retroprosthetic membrane (RPM) surgery becomes necessary. Exceptions would be the rare eye with documented superb recent vision in association with a stable IOL unassociated with any posterior segment abnormalities; for such a high potential eye, confining the implantation to its corneal aspect alone offers the quickest and safest approach. We also prefer the smaller (7.0 mm) backplate for all cases, as it is easier to implant and provides much better access to the posterior segment if later vitrectomy is required. Furthermore, the smaller backplate decreases the risk of iris incarceration. Finally, in contrast to prior practice, we try to avoid the placement of a new glaucoma drainage device (GDD) at the same surgery; despite the rampant glaucoma in this patient group, the additional surgery may create complications that obscure the postoperative determination of visual potential and also may create hypotony, choroidal detachment, and even choroidal hemorrhage in the long term that can, and has, robbed several successful KPro eyes of quite useful vision. That said, we move quickly to insert a GDD in the postoperative period should an elevation in IOP be detected. If a GDD is already in place, we will attempt to flush the tube to determine its viability for IOP control.

Patient Selection/Preoperative Evaluation and Concerns

The eyes most frequently selected for KPro implantation are those that have failed with one or more biological transplants and those eyes with profound disruptions of the ocular surface and limbal stem cell dysfunction such as occurs in ocular chemical injury, Stevens-Johnson syndrome/ toxic epidermal necrolysis, ocular cicatricial pemphigoid, atopy, graft versus host disease, and cicatrizing trauma. An often-overlooked condition potentially amenable to KPro is chronic hypotony in an eye with otherwise useful visual potential. These eyes cannot sustain clarity for a biological graft, but the device is free of this limitation; even "pre-phthisical" eyes have been restored to quite useful vision.[5]

The presurgical evaluation of these patients is complex and ideally incorporates the full complement of information, including visual history, prior surgical procedures and their intraoperative findings, and full eye exam with careful determination of visual field and/or quadrantic light detection as well as intraocular pressure and an ultrasound evaluation. Given the lifelong management requirements with the device, the patient's visual needs and ability to comply with daily care are of critical importance. If KPro implantation is wished but the visual potential of the eye remains indeterminate despite every effort, a small-gauge endoscopy of the posterior segment—either as a brief stand-alone procedure or as a prelude to a full KPro implantation at the same setting—can greatly facilitate determination of the condition of the optic nerve and macula and offer an indication whether it is worth burdening the patient with the device. In extremely rare and perplexing cases, a "trial of PK," though overwhelmingly destined to fail, may provide invaluable information regarding visual potential in the first few weeks after surgery; this may clarify the decision to proceed with device implantation or to spare the patient the burdens of a futile KPro implantation.

Recent advances for these conditions have focused on improving the ocular surface prior to KPro implantation. Lid abnormalities, lid hygiene, and ocular lubrication require careful attention. Eyes should be cultured preoperatively, with a particular focus on *Candida* and other fungi, and colonization should be treated prior to surgery. Certain eyes will benefit from anti-inflammatory therapy prior to surgery. A major advance in the treatment of chemical burns has been prompt administration of anti-tumor necrosis factor-alpha (anti-TNF-α), which has a marked neuroprotective effect and may improve subsequent ocular rehabilitation with KPro.[6]

Intraoperative Procedure and Considerations

Most patients are operated with retrobulbar anesthesia with monitored sedation; general anesthesia is rarely necessary. The exposure of the globe can be as simple as inserting a lid speculum or may require lengthy and meticulous dissection of lid adhesions and surface scar tissue to uncover the corneal surface (see Figure 1). Small-gauge (25- or 27-gauge) vitrectomy is preferred and provides better access in these often scarred and anatomically altered eyes; in eyes with grossly abnormal or indeterminate anatomy, limbal or even corneal cannula placement is required to avoid inadvertent retinal damage. The subsequent surgical sequence is (1) trephination, (2) lens or IOL removal (along with removal of any anterior membranes and retained lenticular material that are oftentimes present [Figure 2]), (3) brief open sky vitrectomy, (4) peripheral iridectomy, and most importantly, (5) intraoperative ophthalmoscopy and/or open sky fundus viewing using the light pipe and microscope,[7] followed by (6) device implantation. When the device is securely sutured, a full pars plana vitrectomy is performed. Although we formerly used the AVI style wide-field contact lenses extensively, the panoramic viewing systems such as the Resight on the Zeiss Lumera operating microscope offer a superb view across the device.

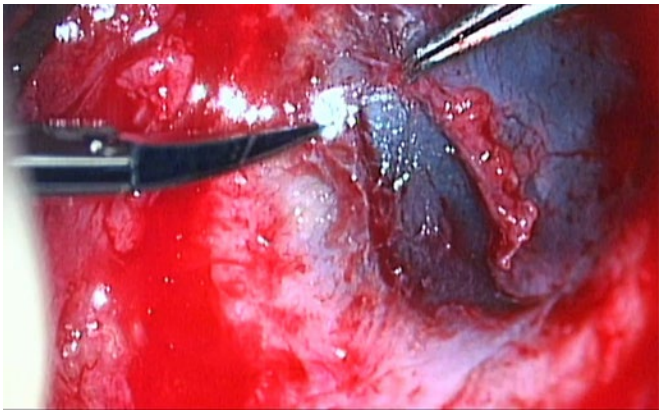


Figure 1. Dissection of extensive corneal pannus 30 years after acute Stevens-Johnson syndrome.

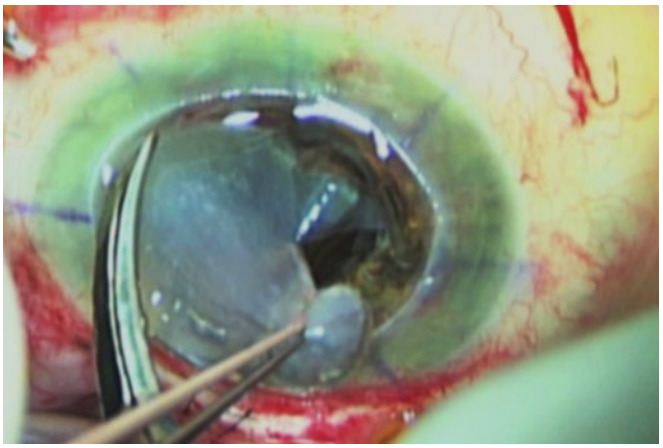


Figure 2. Removal of IOL and residual lens material across the open sky incision.

Intraoperative vitreous hemorrhage may occur from vascularized corneal tissues, surgical wounds, or a vascularized iris. It can be managed by continuing a very low flow through the infusion cannula while the eye is in the open sky state. Retinal detachment may occur with inaccurate cannula placement or overly aggressive vitrectomy, and every care must be taken to avoid it since the management of a detachment at the time of KPro placement is exceptionally challenging at best. Choroidal detachment and hemorrhage of any degree are best prevented by minimizing the time the globe is open and hypotonous, and if these complications occur, their management is similar to that in eyes without a KPro.

Postoperative management benefits greatly from wide-field fundus photography by cameras such as the Optos, which typically provides a magnificent view of the fundus compared to difficulties with indirect ophthalmoscopy.[8] In addition to omnipresent glaucoma, complications include vitreous hemorrhage and retinal detachment in the short term, and RPM, hypotony, vitritis, retinal detachment, macular pucker, endophthalmitis, and wound melting/device extrusion in the long term.[9,10] RPM is the most common complication (roughly 50% of eyes) and is managed by Nd-YAG laser when mild and by vitrectomy when more advanced. Retinal detachment in KPro eyes is invariably accompanied by proliferative vitreoretinopathy and frequently requires the most aggressive techniques, including large retinotomies and subretinal membrane peeling. We avoid operating open sky and have found silicone oil to be a superior tamponade to gas in these eyes. Wound melt/device extrusion have become quite rare with careful attention to the integrity of the ocular surface and use of long-term bandage contact lenses. Similarly, endophthalmitis has also become quite rare since the introduction of long-term topical antibiotic use; most eyes presenting with acute vitritis will prove to be sterile and can be treated by medical therapy. However, a suspicion for infection, including for fungal organisms, must always be maintained, and in this regard, periodic surveillance with conjunctival cultures and treatment of fungal colonization are important. Hypotony can signal the development of phthisis or may be the result of overfiltration of a glaucoma device. In these cases, removing or tying the tube may magically restore an otherwise rapidly deteriorating situation. Macular pucker is managed as appropriate for any eye and is perhaps the only element of vitreoretinal surgery in KPro eyes that is refreshingly straightforward.

Conclusions

Complex ocular rehabilitation with the Boston ("Dohlman") keratoprosthesis continues to improve, with advances in disease understanding, medical therapy, vitreoretinal instrumentation, and improved surgical techniques. Continued research will more successfully bring the benefits of this device to an ever-greater number of visually deserving patients.

References

1. Aravena C, Yu F, Aldave AJ. Long-term visual outcomes, complications, and retention of the Boston type I keratoprosthesis. *Cornea* 2018; 37:3-10.
2. Rudnisky CJ, Belin MW, Guo R, Ciolino JB; Boston Type 1 Keratoprosthesis Study Group. Visual acuity outcomes of the Boston keratoprosthesis type 1: multicenter study results. *Am J Ophthalmol*. 2016; 162:89-98.
3. Fernandez AG, Sippel KC, Ciralsky JB, et al. Boston keratoprosthesis. In: Price FW, McKee Y, eds. *The Digital Manual of Ophthalmic Surgery and Theory*. iBooks; 2014.
4. Srikumaran D, Munoz B, Aldave AJ, et al. Long-term outcomes of Boston type 1 keratoprosthesis implantation: a retrospective multicenter cohort. *Ophthalmology* 2014; 121:2159-2164.
5. Dohlman CH, D'Amico DJ. Can an eye with phthisis be rehabilitated? a case of improved vision with 1-year follow-up. *Arch Ophthalmol*. 1999; 117:123-124.
6. Dohlman CH, Cade F, Regatieri CV, et al. Chemical burns of the eye: the role of retinal injury and new therapeutic possibilities. *Cornea* 2018; 37:248-251.
7. D'Amico DJ. New methods for retinal examination in eyes with a Boston keratoprosthesis. *Retina* 2013; 33:1097-1098.
8. Kornberg DL, Yannuzzi NA, Klufas MA, D'Amico DJ, Orlin A, Kiss S. Ultra-widefield imaging of posterior segment in the setting of Boston keratoprosthesis. *Retina* 2016; 36:1101-1110.
9. Klufas MA, Yannuzzi NA, D'Amico DJ, Kiss S. Vitreoretinal aspects of permanent keratoprosthesis. *Surv Ophthalmol*. 2015; 60:216-228.
10. Kiang L, Sippel KC, Starr CE, et al. Vitreoretinal surgery in the setting of permanent keratoprosthesis. *Arch Ophthalmol*. 2012; 130:487-492.

Management of Fellow Eyes of Patients With Nontraumatic Giant Retinal Tears

Harry W Flynn Jr MD and Jesse D Sengillo MD

I. Giant Retinal Tears

A. Definition: Full-thickness retinal breaks involving at least 3 clock hours (90 degrees) of the retina with or without retinal detachment

B. Risk factors for nontraumatic giant retinal tears

1. Myopia
2. Lattice degeneration
3. Anterior segment surgery
4. Inherited vitreoretinopathy

C. Clinical images (see Figures 1 and 2)

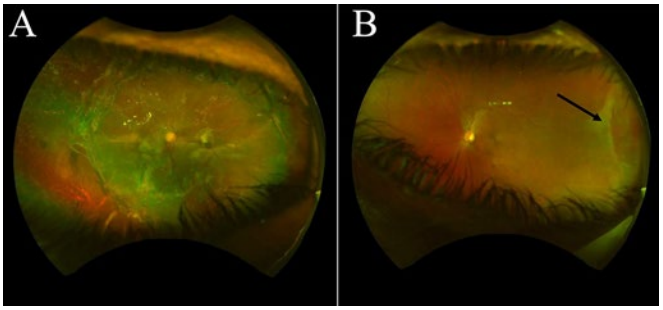


Figure 1. Patient with a retinal detachment due to a nontraumatic giant retinal tear in the right eye after surgical repair (A) and an asymptomatic retinal break in the left eye (B).

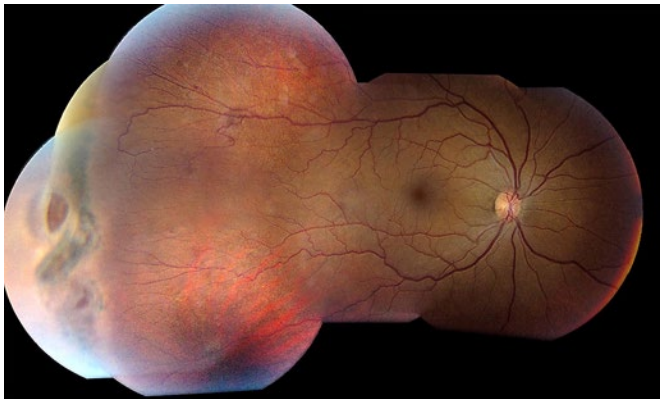


Figure 2. Patient with an asymptomatic retinal break and associated retinal detachment in the right eye (shown) and a history of retinal detachment due to a nontraumatic giant retinal tear in the left eye (not shown).

II. Previously Reported Rates of Retinal Breaks and Retinal Detachments in Fellow Eyes

A. Landmark studies: Schepens (1962)[1] and Freeman (1978)[2]

B. Literature review

Table 1. Selected Literature Assessing Outcomes of Fellow Eyes of Nontraumatic Giant Retinal Tears

Reference (year)	No. of Patients	Fellow Eye Findings	Follow-up Length	Comment
Schepens et al (1962)[1]	122	3 (2.5%) GRT 19 (16.0%) "predetachment" 33 (28.0%) RD	Not specified	
Glasspool et al (1973)[6]	56	5 (9%) GRT 17 (30%) "pre-detachment lesions" 16 (29%) RD	Not specified	
Kanski et al (1975)[7]	68	14.7% "predisposing lesions" 42.6% RD	Not specified	Included traumatic GRTs
Freeman et al (1978)[2]	226	12.8% GRT 22.5% breaks 15.9% RD	44 months	55 patients underwent prophylactic SB or cryotherapy and are included in rates.
Wolfensberger et al (2003)[8]	48	2.1% GRT 2.1% breaks 4.2% RD	84 months	All fellow eyes underwent 360 degrees cryotherapy
Ghosh et al (2004)[9]	29	10.3% GRT No breaks No RD	28 months	18 fellow eyes underwent 360 laser or cryotherapy. 1 patient (Stickler syndrome) had bilateral RDs at presentation.
Al-Khairi et al (2008)[10]	89	28.2% breaks 16.7% RD	30 months	Prior history of fellow eye findings included in rates
Lee et al (2009)[11]	96	3.2% GRT 9.7% breaks 12.9% RD	63 months	
Ang et al (2010)[12]	41	2.4% GRT 7.3% breaks 2.4% RD	12 months	
Ripandelli et al (2016)[13]	160	16.5% GRT 14.4% RD	44 months	
Verhoekx et al (2020)[14]	129	26.1% GRT 15.5% breaks 30.1% RD	107 months	78 patients underwent prophylactic 360 laser Decreased macula-off RD rate in the treatment group
Sengillo et al (2021)[5]	51	2% GRT 12% breaks 18% RD	83 months	

Abbreviations: GRT, giant retinal tear; RD, retinal detachment; SB, scleral buckle.

III. Studies at Our Institution (Bascom Palmer Eye Institute)

A. Gonzalez et al (2013)[3]—fellow eye outcomes not reported

B. Rodriguez et al (2018)[4]—fellow eye outcomes not reported

C. Sengillo (2021)[5] —study of fellow eyes

IV. Management Options for Fellow Eyes

A. Observation

B. Cryotherapy

C. Laser retinopexy

V. Conclusions: Fellow Eyes of Patients With Nontraumatic Giant Retinal Tears

A. Retinal breaks/detachments are commonly identified in fellow eyes of patients with prior nontraumatic giant retinal tears.

B. Role of prophylactic treatment in fellow eyes is controversial and can be made on a case-specific basis.

C. Patient education and regular follow-up examinations are recommended.

References

1. Schepens CL, Dobie JG, McMeel MJ. Retinal detachments with giant breaks: preliminary report. *Trans Am Acad Ophthalmol Otolaryngol*. 1962; 66:471-479.
2. Freeman HM. Fellow eyes of giant retinal breaks. *Trans Am Ophthalmol Soc*. 1978; 76:343-382.
3. Gonzalez MA, Flynn HW Jr, Smiddy WE, Albini TA, Berrocal AM, Tenzel P. Giant retinal tears after prior pars plana vitrectomy: management strategies and outcomes. *Clin Ophthalmol*. 2013; 7:1687-1691.
4. Rodriguez M, Lin J, Townsend JH, et al. Giant retinal tears: clinical features and outcomes of vitreoretinal surgery at a university teaching hospital (2011-2017). *Clin Ophthalmol*. 2018; 12:2053-2058.
5. Sengillo JD, Yannuzzi NA, Smiddy WE, Flynn HW Jr; the Giant Retinal Tear Study Group. Giant retinal tears: outcomes of fellow eyes. *Ophthalmology* (submitted).
6. Glasspool MG, Kanski JJ. Prophylaxis in giant tears. *Trans Ophthalmol Soc U K*. 1973; 93(0):363-371.
7. Kanski JJ. Giant retinal tears. *Am J Ophthalmol*. 1975; 79(5):846-852.
8. Wolfensberger TJ, Aylward GW, Leaver PK. Prophylactic 360 degrees cryotherapy in fellow eyes of patients with spontaneous giant retinal tears. *Ophthalmology* 2003; 110(6):1175-1177.
9. Ghosh YK, Banerjee S, Savant V, et al. Surgical treatment and outcome of patients with giant retinal tears. *Eye (Lond)*. 2004; 18(10):996-1000.
10. Al-Khairi AM, Al-Kahtani E, Kangave D, Abu El-Asrar AM. Prognostic factors associated with outcomes after giant retinal tear management using perfluorocarbon liquids. *Eur J Ophthalmol*. 2008; 18(2):270-277.
11. Lee SY, Ong SG, Wong DW, Ang CL. Giant retinal tear management: an Asian experience. *Eye (Lond)*. 2009; 23(3):601-605.
12. Ang GS, Townend J, Lois N. Epidemiology of giant retinal tears in the United Kingdom: the British Giant Retinal Tear Epidemiology Eye Study (BGEES). *Invest Ophthalmol Vis Sci*. 2010; 51(9):4781-4787.
13. Ripandelli G, Rossi T, Cacciamani A, Scarinci F, Piaggi P, Stirpe M. Laser prophylactic treatment of the fellow eye in giant retinal tears: long-term follow-up. *Retina* 2016; 36(5):962-966.
14. Verhoekx JSN, van Etten PG, Wubbels RJ, van Meurs JC, van Overdam KA. Prophylactic laser treatment to decrease the incidence of retinal detachment in fellow eyes of idiopathic giant retinal tears. *Retina* 2020; 40(6):1094-1097.

Tips for Handling Complex Retinal Detachments

Dean Eliott MD

I. Proliferative Vitreoretinopathy

A. Preretinal membranes: Attempt complete removal; peeling from disc outward is an effective technique.

B. Ciliary body membranes: Aphakia/pseudophakia enables epiciliary membrane peeling and results in less postoperative hypotony.

C. Subretinal membranes: Consider observation if not exerting significant traction (especially true in young patients); otherwise, attempt removal with retinotomy or retinectomy.

D. Retinal contraction: If unrelieved traction despite scleral buckle, consider retinectomy (see below).

II. Fovea Splitting Retinal Detachment (RD)

For superior RD with the inferior edge at or near the fovea, attempt to remove all subretinal fluid to prevent a postoperative fold through the macula; since this is not always possible, immediate and strict postoperative face-down (or temporal side-down) positioning is recommended.

III. Giant Retinal Tear (GRT)

A. Consider buckle if edge of GRT is inferiorly located.

B. Prevent retinal slippage during perfluorocarbon fluid–air exchange by performing slow and meticulous aspiration along edge of tear so that vitreous base dehydrates; or avoid fluid–air exchange by performing direct perfluorocarbon–silicone oil exchange.

C. In nontraumatic cases of GRT, prophylactic treatment of the fellow eye may be considered.

IV. Retinoschisis

A. Without RD: Surgery is indicated very rarely unless fovea is involved.

B. With RD: Consider surgery if progresses toward fovea and is symptomatic, if fovea is already involved, or if full-thickness retinal tear is present; RD due to inner and outer breaks progresses slowly; inner wall retinectomy is often used since an irreversible absolute scotoma is already present in area of schisis.

V. Macular Hole With RD

A. If no peripheral break is visible, use perfluorocarbon liquid to confirm.

B. If internal limiting membrane (ILM) peeling is performed, consider initiating peel in papillomacular bundle and peeling toward the hole (since retinal attachment at disc provides some countertraction and minimizes retinal mobility in this area).

VI. Serous RD With Optic Disc Pit

A. Consider a period of observation since some resolve spontaneously.

B. A variety of surgical techniques have been proposed; if performing endolaser to edge of disc, nerve fiber layer damage can be avoided/minimized if laser is done prior to fluid–air exchange.

VII. Infectious Retinitis With RD

A. Acute retinal necrosis and other forms of retinitis may result in multiple retinal breaks in areas of retinal necrosis; vitreoretinal traction may not be present.

B. Silicone oil is typically used, and a scleral buckle is not typically placed.

VIII. Retinal Macrocyst

Repair RD in usual manner and macrocyst will usually resolve.

IX. General Principles

A. Retinotomy: creating a hole in the retina (retinal incision only, no excision)

1. Drainage retinotomy: to remove subretinal fluid (Drainage site is located posteriorly when perfluorocarbon liquid is not used to reattach the retina; drainage site is located anteriorly when perfluorocarbon use results in anteriorly loculated subretinal fluid.)

2. Access retinotomy: to remove choroidal neovascular membrane (CNVM), subretinal hemorrhage, subretinal membranes/bands, retained subretinal perfluorocarbon liquid, subretinal foreign body, or to inject drugs (tissue plasminogen activator)/stem cells/viral vectors for gene therapy

B. Retinectomy: excision of retina

1. Removal of anterior flap of retinal tear in primary RD

2. Removal of retinal incarceration in traumatic or surgical wound

3. Removal of fibrotic, contracted retina in proliferative vitreoretinopathy (PVR) or proliferative diabetic retinopathy (PDR)

C. Retinectomy surgical technique: general guidelines
   1. Lensectomy in phakic eyes
   2. Consider scleral buckle to support vitreous base (except in cases with 360-degree retinectomy or with 360-degree extensive peripheral laser)
   3. Retinectomy performed after attempted complete epiretinal membrane removal; if retinectomy is done before complete epiretinal membrane removal, further epiretinal membrane removal may be difficult.
   4. Orientation: circumferential, posterior to vitreous base
   5. Location: Avoid retinectomy edge near 6 o'clock position; most common retinectomy location is inferiorly with edges at approximately 3 o'clock and 9 o'clock.
   6. Size: Retinectomy should extend into normal retina surrounding areas of traction; most common retinectomy size is 6 clock hours or 180 degrees; if greater than 270 degrees, extend the retinectomy to 360 degrees.
   7. Hemostasis: diathermy used to delineate intended edge and to prevent intraoperative bleeding
   8. Instruments: vitrectomy probe (or scissors) used to cut retina
   9. Adjuvants: may consider perfluorocarbon liquid to stabilize posterior retina
   10. Complete excision of anterior retina to prevent postoperative proliferation with resultant traction on the retinectomy edge or ciliary body
   11. Retinopexy: confluent endolaser to the retinectomy edge
   12. Extended tamponade: C_3F_8 gas or silicone oil (Silicone Oil Study showed equal efficacy in eyes with retinectomy; recent studies favor silicone oil over gas; redetachment occurs in 4%-25% after oil removal.)

D. Incidence of retinectomy
   1. PVR
      a. Early studies: retinectomy performed in 2%-8%
      b. Silicone Oil Study (1993): retinectomy performed in 29% overall
         i. Group 1 (no previous vitrectomy): retinectomy performed in 20%
         ii. Group 2 (previous vitrectomy): retinectomy performed in 42%
      c. Recent studies: retinectomy performed more commonly, in up to 64%
   2. PDR
      a. Primary vitrectomy: retinectomy performed in 5%
      b. Reoperation vitrectomy: retinectomy performed in 25%

E. Complications of retinectomy
   1. Hemorrhage: usually due to incomplete diathermy; postoperative fibrous proliferation may occur in areas of blood.
   2. Hypotony: Reported in 2%-43% after 180 to 360-degree retinectomy and in 17%-20% after 360-degree retinectomy; retinectomy exposes retinal pigment epithelium (RPE) and allows posterior outflow and absorption of intraocular fluid by the choroid; recurrent fibrous proliferation with resultant ciliary body traction may also lead to hypotony (PVR surgery in aphakic/pseudophakic eyes should include epiciliary membrane peeling to relieve ciliary body traction.)
   3. Visual field defect
   4. Recurrent fibrous proliferation: Surgery for macular pucker reported in 22%-43%; severe fibrous proliferation may lead to recurrent RD and/or hypotony.
   5. Persistent traction: occurs when size of retinectomy is inadequate
   6. RPE/choroidal damage: may occur when excising retina in area of shallow detachment
   7. Retained subretinal perfluorocarbon: more likely to occur in cases with large retinectomy (less common since development of small gauge vitrectomy with valved cannulas); consider saline rinse
   8. Neovascularization: CNVM may rarely occur at edge of retinectomy; anterior retinal and/or iris neovascularization may occur when anterior retina is incompletely excised.

F. Retinectomy in PDR
   1. Small posterior focal retinectomy: to relieve persistent traction on pre-existing or iatrogenic breaks
   2. Large peripheral retinectomy: to remove massive fibrous proliferation caused by severe ischemia

References

1. Schepens CL, Dobble JG, Mc MJ. Retinal detachments with giant breaks: preliminary report. *Trans Am Acad Ophthalmol Otolaryngol*. 1962; 66:471-479.
2. Machemer R. Retinotomy. *Am J Ophthalmol*. 1981; 768-774.
3. Machemer R, McCuen BW, de Juan E. Relaxing retinotomies and retinectomies. *Am J Ophthalmol*. 1986; 102:7-12.

4. Byer NE. Long-term natural history study of senile retinoschisis with implications for management. *Ophthalmology* 1986; 93:1127-1137.
5. Blumenkranz MS, Azen SP, Aaberg TM, et al.; Silicone Study Group. Relaxing retinotomy with silicone oil or long-acting gas in eyes with severe proliferative vitreoretinopathy (Silicone Study Report #5). *Am J Ophthalmol*. 1993; 116:557-564.
6. Tseng JJ, Barile GR, Schiff WM, Akar Y, Vidne-Hay O, Chang S. Influence of relaxing retinotomy on surgical outcomes in proliferative vitreoretinopathy. *Am J Ophthalmol*. 2005; 140:628-636.
7. Quiram PA, Gonzales CR, Hu W, et al. Outcomes of vitrectomy with inferior retinectomy in patients with recurrent rhegmatogenous retinal detachments and proliferative vitreoretinopathy. *Ophthalmology* 2006; 113:2041-2047.
8. Tsui I, Schubert HD. Retinotomy and silicone oil for detachments complicated by anterior inferior proliferative vitreoretinopathy. *Br J Ophthalmol*. 2009; 93:1228-1233.
9. Jain N, Johnson MW. Pathogenesis and treatment of maculopathy associated with cavitary optic disc anomalies. *Am J Ophthalmol*. 2014; 158:423-435.
10. Liu TYA, Vizcaino MA, Eberhart CG, Sachdeva MM. Association of macular and peripheral retinal macro-pseudocysts with chronic retinal detachment. *JAMA Ophthalmol*. 2018; 136:956-958.

Management of Vision-Obscuring Vitreous Hemorrhage Associated With Posterior Vitreous Detachment: Observe or Operate?

Gaurav K Shah MD and Gautam Vangipuram MD

I. Vitrectomy for Treatment of Retinal Tears
   A. Vitreous hemorrhage (VH) is a known risk factor for retinal tears in patients with acute posterior vitreous detachment.
   B. Retinal tears in nondiabetic VH: Incidence ranges from 61% to 72%.[1-2]
   C. Diagnostic utility of ultrasound to detect retinal pathology is inadequate, with sensitivity for detecting retinal breaks and retinal detachments as low as 24.3% and 58.5%, respectively.[3]
   D. Outcomes of early vs. delayed vitrectomy for nondiabetic VH: Superior visual outcomes achieved in early vitrectomy[3]

II. Surgical Technique for Repair of Retinal Detachment With Associated VH
   A. VH is a risk factor for the development of proliferative vitreoretinopathy (PVR). Platelet-derived growth factors (PDGF) and fibronectin (FN) found in serum aid retinal pigment epithelial migration in development of PVR.[5]
   B. Outcomes for VH associated with retinal detachment
      1. Scleral buckle helpful in preventing postoperative PVR
      2. Pars plana vitrectomy/scleral buckle provides superior anatomical and visual outcomes compared to PPV alone.

III. Increasing prevalence of high myopia may predispose eyes to more severe PVD-related pathology.[4]

References

1. El-Sanhouri AA, Foster RE, Petersen MR, et al. Retinal tears after posterior vitreous detachment and vitreous hemorrhage in patients on systemic anticoagulants. *Eye (Lond)*. 2011; 25(8):1016-1019.
2. Sarrafizadeh R, Hassan TS, Ruby AJ, et al. Incidence of retinal detachment and visual outcome in eyes presenting with posterior vitreous separation and dense fundus-obscuring vitreous hemorrhage. *Ophthalmology* 2001; 108(12):2273-2278.
3. Connors D, Shah G, Blinder K, Dang S. Early versus delayed vitrectomy for nondiabetic vitreous hemorrhage. *J VitreoRetin Dis*. 2018; 2(2):87-90.
4. Hayashi K, Manabe SI, Hirata A, Yoshimura K. Posterior vitreous detachment in highly myopic patients. *Invest Ophthalmol Vis Sci*. 2020; 61(4):33.
5. Campochiaro PA, Jerdan JA, Glaser BM. Serum contains chemoattractants for human retinal pigment epithelial cells. *Arch Ophthalmol*. 1984; 102(12):1830-1833.

Table 1. Comparing Single-Surgery Anatomical Success Rates Between PPV and PPV/SB in Repair of Retinal Detachment With Associated Vitreous Hemorrhage

	PPV, No. (%)	PPV/SB, No. (%)	Odds Ratio (95% CI)[a]	*P*-Value
All eyes	107 (77.5)	78 (91.8)	0.31 (0.11-0.77)	.006
Phakic	62 (79.5)	55 (88.7)	0.50 (0.16-1.39)	.172
PC-IOL	44 (77.2)	23 (100)	0.00 (0.00-0.71)	.015
C_3F_8	37 (72.5)	42 (89.4)	0.32 (0.08-1.05)	.043
SF_6	61 (82.4)	24 (96)	0.20 (0.00-1.46)	.110
Oil	3 (60.0)	10 (90.9)	0.17 (0.00-4.39)	.214

Abbreviations: PPV, pars plana vitrectomy; PPV/SB, combined pars plana vitrectomy and scleral buckle; PC-IOL, posterior chamber IOL; C_3F_8, perfluoropropane; SF_6, sulfur hexafluoride.

[a]Analyzed for the risk of a retinal redetachment in reference to PPV alone.

Vitrectomy for Diabetic Traction Retinoschisis

Stanley Chang MD, Tarun Sharma MD, Wayne S Fuchs MD, and Liang Han MD

Introduction

Diabetic traction retinoschisis received little attention until the widespread use of spectral domain OCT. The clinical findings of this condition were reported by Lincoff, who did careful biomicroscopic funduscopic examinations of tractional elevations in patients with diabetic retinopathy. In 200 eyes with tractional elevations, he found that approximately 19.5% had predominantly traction retinoschisis (TRS), but that up to 42.5% (85 eyes) had some element of TRS.[1]

Our understanding of traction retinoschisis progressed slowly. The histopathology of TRS was described in 4 postmortem eyes with proliferative diabetic retinopathy using a special thick-section technique. There were areas of adhesion of the posterior hyaloidal membrane to the retina, and areas of traction retinal detachment, TRS, and combined traction retinal detachment (TRD) and TRS.[2] With the development of spectral domain OCT, it was much easier to differentiate areas of retinoschisis from detachment, and in 1 series of 17 consecutive eyes, TRS was found in 16 (94%), whereas TRD was found in 6 eyes (34%).[3]

A larger series of patients with diabetic TRS (n = 32) and TRD (n = 32) was studied longitudinally by OCT, before and after vitrectomy. The authors concluded that eyes with TRS tended to less thickened fibrovascular proliferation and tended to be less vascularized than eyes with TRD. Macular changes induced by TRS were inner layer cysts, lamellar macular holes, and foveal detachment. They also reported that visual acuity (VA) improved following vitrectomy in both groups, and the difference was not statistically significant.[4]

Case Presentations

Two cases of vitrectomy for diabetic TRS involving the macula are presented. Both cases had TRS, with the typical columnar stretching of Müller fibers within the retina. In the first case, a 61-year-old woman with a macular hole in the fellow eye underwent a combined phacoemulsification/IOL, and vitrectomy with membrane peeling was done. Triamcinolone was used to stain the vitreous cortex that was adherent to the macula. Three months postoperatively, the VA was corrected to 20/40, and at 1 year, the VA was 20/25. In the second case, a 66-year-old patient with long-standing traction elevation of the right eye was seen with VA 20/200. Following vitrectomy, the VA improved to 20/80.

In both of these patients, the height of the macular elevation is exaggerated by the OCT study, in which the vertical scale is maximally 2 mm, in contrast to the length of the scan, which is 6 mm. As a result, these macular elevations are relatively low. The other common finding was that the peripheral hyaloid membrane was shallowly separated or remained adherent to the retina. The broad adhesion of the peripheral hyaloid limits the traction of the macula that would result in stronger tractional forces that cause TRD.

References

1. Lincoff H, Serag Y, Chang S, Silverman R, Bondok B, El-Aswad M. Tractional elevations of the retina in patients with diabetes. *Am J Ophthalmol*. 1992; 113:235-242.
2. Faulborn J, Ardjoman N. Tractional retinoschisis in proliferative diabetic retinopathy: a histopathological study. *Graefes Arch Clin Exp Ophthalmol*. 2000; 238:40-44.
3. Imai M, Iijima H, Hanada N. Optical coherence tomography of traction macular elevations in eyes proliferative diabetic retinopathy. *Am J Ophthalmol*. 2001; 132:81-84.
4. Su CC, Yang CH, Yeh PT, Yang CM. Macular tractional retinoschisis in proliferative diabetic retinopathy: clinical characteristics and surgical outcome. *Ophthalmologica* 2014; 231:23-30.

Submacular Hemorrhage: Surgical Indications and Technique

Sophie J Bakri MD

NOTES

Giant Internal Limiting Membrane Tears: Pathogenesis, Clinical Characteristics, and Surgical Utility

Mark W Johnson MD, Asad F Durrani MD, and Robert A Hyde MD PhD

I. Giant Tears of the Internal Limiting Membrane (ILM): Background and Definition

A. Large tears of the ILM associated with epiretinal membrane (ERM):

1. Are commonly present in symptomatic patients
2. Often go unrecognized
3. Are rarely discussed and incompletely characterized in the literature

B. The purpose of this study was to evaluate the following aspects of giant ILM tears:

1. Prevalence
2. Clinical features
3. Pathogenesis
4. Surgical utility

C. We defined a giant ILM tear as an ILM dehiscence that is sufficiently large to result in an elevated and scrolled ILM edge.

II. Methods

A. Retrospective review of patients with ERM that underwent surgery by a single surgeon over 4 years (2016-2019)

B. Demographic, clinical, and imaging data were collected from the medical record.

C. The study was approved by the IRB of the University of Michigan.

III. Results

A. Prevalence

Giant ILM tears were found in 32.4% of eyes with ERM that underwent surgery (23/71).

B. Characteristics

1. High myopia was seen in 26.1% of eyes with giant ILM tears compared to 8.3% of eyes without ($P = .055$).
2. Eyes with and without giant ILM tears showed no differences with respect to other studied characteristics (eg, age, sex, pre- and postoperative visual acuity, macular thickness, presence of posterior vitreous detachment [PVD], lens status, and visual symptoms)
3. Average length of torn ILM edge was 5.57 (± 0.43) mm.
4. Use of radial OCT scans increased the preoperative detection rate.
5. Associated features
   a. Nerve fiber layer schisis under ERM or adjacent to torn ILM edge (87% of eyes)
   b. Inner retinal dimpling within ILM dehiscence (35.8% of eyes)
   c. Paravascular red lesions (retinal "stretch marks") of 2 types
      i. intraretinal cavitations
      ii. inner lamellar retinal defects

IV. Pathogenesis

A. Bovey and Uffer (2008) suggested that large ILM dehiscences might be caused by vitreoretinal traction during PVD.

B. However, several lines of evidence suggest that ERM contracture is the primary pathogenic mechanism.

1. Giant ILM tears:
   a. Have not been reported in eyes with PVD but without ERM
   b. Are not seen in eyes with mild, minimally-contracted ERM
   c. Are always located at the edge of a contracted ERM
   d. Have been observed to develop coincident with increased ERM contracture
2. Curvature analysis shows that the edge of a giant ILM tear is virtually always convex, pointing toward the center of ERM contracture.

C. ILM dimpling seen within an area of ILM dehiscence is analogous to dimpling seen after surgical ILM peeling.

1. Likely results from Müller cell injury
2. Not always present, since dimples take time to develop

D. Retinal nerve fiber layer schisis and paravascular red lesions ("stretch marks" along relatively rigid blood vessels) provide additional evidence for substantial ERM contracture in these eyes.

V. Surgical Utility

A. In all cases that employed Brilliant Blue G staining (n = 19), the suspected ILM tear was confirmed.

B. In all these cases, the scrolled edge of ILM was used as a convenient and safe handle to initiate peeling of the ILM and overlying ERM.

VI. Conclusions

A. Giant tears of the ILM are not uncommonly present in eyes with surgical ERMs, especially in highly myopic eyes.

B. Radial OCT scans and recognition of associated features may assist in their identification.

C. ERM contracture is the likely the predominant pathogenic mechanism in ILM tear formation. An initiating role for vitreoretinal traction along retinal vessels cannot be excluded in a subset of eyes.

D. The scrolled edge of an ILM tear provides a convenient and safe "handle" to initiate peeling of the ILM and overlying ERM.

Selected Readings

1. Bovey EH, Uffer S. Tearing and folding of the retinal internal limiting membrane associated with macular epiretinal membrane. *Retina* 2008; 28(3):433-440.
2. Hussnain SA, Sharma T, Hood DC, Chang, S. Schisis of the retinal nerve fiber layer in epiretinal membranes. *Am J Ophthalmology*. 2019; 207:304-312.
3. Amouyal F, Shah SU, Pan CK, Schwartz SD, Hubschman J-P. Morphologic features and evolution of inner retinal dimples on optical coherence tomography after internal limiting membrane peeling. *Retina* 2014; 34(10):2096-2102.
4. Wubben TJ, Johnson MW. Inner retinal dimpling after endophthalmitis and vitrectomy without internal limiting membrane peeling. *JAMA Ophthalmol*. 2020; 138:218-221.
5. Pichi F, Lembo A, Morara M, et al. Early and late inner retinal changes after inner limiting membrane peeling. *Int Ophthalmol*. 2014; 34(2):437-446.
6. Shimada N, Ohno-Matsui K, Nishimuta A, et al. Detection of paravascular lamellar holes and other paravascular abnormalities by optical coherence tomography in eyes with high myopia. *Ophthalmology* 2008; 115(4):708-717.

New Strategies to Treat Myopic, Chronic, and Persistent Macular Holes

John T Thompson MD

I. The success for closing typical idiopathic macular holes is over 90% in most series, with improved visual acuity in over 70% of eyes, yet some macular holes remain challenging to close using traditional internal limiting membrane (ILM) removal.

II. New techniques have been recently reported to assist in closing more difficult macular holes.

A. Three categories of macular holes appear to have higher visual and anatomic success with these newer techniques.

1. Persistent macular holes that have failed 1 or more prior surgeries

2. Macular holes in eyes with high myopia which are often associated with posterior staphylomas, retinal detachment, or myopic macular schisis

3. Large, chronic macular holes of 2 years or greater duration

B. There are 3 special techniques to consider in treating these macular holes with poorer prognosis for closure:

1. Internal limiting membrane flap techniques

a. This was initially described by Michalewska for treating large macular holes.[1] There are a number of variations, but the basic technique is to partially peel and then reflect the ILM over the macular hole while the ILM is still attached to the retina near the rim of the macular hole, creating a flap. The ILM can be reflected from all around the macular hole or from temporal, superior, or nasal to the macular hole.[2,3]

b. The goal is to have the ILM bridge the macular hole while the gas bubble is large, so it forms a scaffold for migration of glial cells to close the macular hole.

c. A longer-acting gas bubble or silicone oil may be used to help improve the likelihood of macular hole closure.

d. The success rate with use of the ILM flap technique in these more challenging macular holes was superior to ILM peeling alone in several larger comparative studies.[4-6] One representative study reported closure of 81% of macular holes associated with retinal detachment, with the ILM flap group showing improved acuity (20/160+1) compared to the ILM peel group (20/200).[6]

2. Autologous retinal transplant

a. Initially described by Grewel and Mahmoud for myopic macular holes[7]

b. A piece of neurosensory retina is cut out from the midperipheral retina and shifted into the macular hole beneath perfluorocarbon liquid bubble to avoid losing or inverting the transplanted retina plug. Macular hole closure has been successful with subretinal positioning and preretinal positioning of the transplant in multicenter studies from a variety of investigators.[8]

c. Tamponade to keep the free autologous retinal flap from dislocating has been performed using gas, silicone oil, or short-term perfluorocarbon liquid.

d. Macular hole closure was achieved in 89% of eyes with prior failed macular hole closure or macular hole retinal detachment, with visual acuity improvement of 3 lines or better in 43% of eyes.[8]

3. Amniotic membrane transplant

a. Initially described by Rizzo and Caporossi for persistent and myopic macular holes[9,10]

b. A piece of amniotic membrane is cut and inserted into the subretinal space of the macular hole such that the chorion layer with villi is in apposition to the retinal pigment epithelium.

c. The authors used relatively short-acting SF_6 or air tamponade, in contrast to other techniques above using longer-acting tamponade.

d. Macular hole closure was successful in 8 of 8 eyes in a pilot series and 94% in a series of 16 eyes.[9,10]

III. There have not been any larger randomized studies comparing the ILM flap, autologous retinal transplant, and amniotic membrane transplant since each technique has been evolving with increasing surgeon experience and dissemination into the community.

A. The ILM flap technique is more straightforward and may be preferred in eyes where there is adequate staining of the ILM and sufficient ILM to cover the macular hole.

B. The autologous retinal transplant and amniotic membrane transplant techniques should be considered in eyes where an ILM flap cannot be created, and each yield relatively good anatomic results with modest visual acuity improvement.

C. Further studies should better define the optimal treatment of difficult-to-close persistent and large chronic macular holes, as well as those related to high myopia.

References

1. Michalewska Z, Michalewski J, Adelman RA, Nawrocki J. Inverted internal limiting membrane flap technique for large macular holes. *Ophthalmology* 2010; 117(10):2018-2025.
2. Tabandeh H, Morozov A, Rezaei KA, Boyer DS. Superior wide-base internal limiting membrane flap transposition (SWIFT) for macular holes—flap status and outcomes. *Ophthalmol Retina*. 2021; 5(4):317-323.
3. Chou HD, Chong YJ, Teh WM, et al. Nasal or temporal internal limiting membrane flap assisted by sub-perfluorocarbon viscoelastic injection for macular hole repair. *Am J Ophthalmol*. 2020; 223:296-305.
4. Michalewska Z, Michalewski J, Dulczewska-Cichecka K, Adelman RA, Nawrocki J. Temporal inverted internal limiting membrane flap technique versus classic inverted internal limiting membrane flap technique: a comparative study. *Retina* 2015; 35(9):1844-1850.
5. Marques RE, Sousa DC, Leal I, Faria MY, Marques-Neves C. Complete ILM peeling versus inverted flap technique for macular hole surgery: a meta-analysis. *Ophthalmic Surg Laser Imaging Retina*. 2020; 51(3):187-192.
6. Matsumae H, Mirizane Y, Yamane S, et al. Inverted internal limiting membrane flap versus internal limiting membrane peeling for macular hole retinal detachment in high myopia. *Ophthalmol Retina*. 2020; 4(9):919-926.
7. Grewal D, Mahmoud TH. Autologous neurosensory retinal free flap for closure of refractory myopic macular holes. *JAMA Ophthalmol*. 2016; 134(2):229-230.
8. Moysidis SN, Koulisis, Andrean S, et al. Autologous retinal transplantation for primary and refractory macular holes and macular hole retinal detachments: the global consortium. *Ophthalmology* 2021; 128(5):672-685.
9. Rizzo S, Caporossi T, Tartaro, et al. A human amniotic membrane plug to promote retinal breaks repair and recurrent macular hole closure. *Retina* 2019; 39 Suppl 1:S95-103.
10. Caporossi T, Pacini B, De Angelis L, et al. Human amniotic membrane to close recurrent, high myopic macular holes in pathologic myopia with axial length of ≥30 mm. *Retina* 2020; 40(10):1946-1954.

Vitreoretinal Surgery Panel

Panel Moderator: H Richard McDonald MD

Panelists: Sophie J Bakri MD, Jonathan Chang MD, Dean Eliott MD, John T Thompson MD

NOTES

A Multicountry Analysis of the Effect of COVID-19 on Outcomes of VEGF Inhibitor Therapy

Mark Gillies MD PhD, Daniel Barthelmes MD PhD, Javier Zarranz-Ventura MD PhD FEBO

The SARS-CoV2 outbreak causing COVID-19 disease started in November 2019 in Wuhan, China, and quickly spread overseas, becoming a global pandemic and challenging health-care systems around the world.[1] Efforts to mitigate the spread of COVID-19 may have caused treatment delays in chronic diseases of many specialties, especially during lockdown periods if all nonessential activities were stopped and only emergencies were attended in health-care centers, as recommended by national and international societies.[2,3] Intravitreal therapy was prioritized and, in particular, patients with neovascular AMD (nAMD) were treated first, followed by eyes with diabetic macular edema (DME) and retinal vein occlusion (RVO).[2] Despite this, recent studies have reported decreased adherence to treatment visits for several reasons, including patients' fear and public transport limitations. The real clinical impact of these delays still needs to be elucidated, particularly as countries differed in their response and in the severity of the pandemic.

The recent advent of EHR and web-based tools has facilitated the collection of large amounts of structured data from multiple centers, often internationally. The Fight Retinal Blindness! (FRB!) database is an international, prospectively designed registry that has provided useful data on clinical outcomes of anti-VEGF therapies and optimal treatment.[4] This study evaluated the impact of COVID-19 pandemic lockdown on intravitreal therapy outcomes in a large international cohort of AMD, DME, and RVO eyes treated during the first wave of the pandemic. Intercountry differences were also explored in order to identify potential reasons for these variations, which may help clinicians to prepare strategies to mitigate vision loss in future pandemics.

The baseline visit was defined as the last visit within 3 months prior to the lockdown, with pre- and postlockdown periods defined as 6 months before and after the baseline date. A total of 5782 eyes across Australia, France, Ireland, Italy, Netherlands, New Zealand, Spain, and Switzerland were included. Eyes with nAMD (n = 4649) generally lost vision (–3.8 to –0.4 letters) at 6 months in all countries, with some experiencing only mild vision loss (≤1 letter loss: Australia, France, the Netherlands, and New Zealand) and others with moderate vision loss (>1 letter loss: Ireland, Italy, and Spain). These correlated with a greater reduction in injections, with a reduction of only 1 injection compared to the 6 months prior to the baseline visit observed in Australia, France, and the Netherlands, and a reduction of 2 injections in those with worse outcomes like Ireland, Italy, and Spain. Notably, the first postlockdown injection interval was greatly extended, suggesting at least 1 missed injection in many patients likely due to cancellations and rescheduling of appointments, with Spain having the longest initial postlockdown treatment interval.

Lockdowns had a slightly different impact on clinical outcomes in eyes with DME (n = 654) and RVO (n = 479). The number of injections for DME decreased by 1 (Australia, France, Spain) or >1 injection (Italy, Ireland, New Zealand, Switzerland) in the 6 months after the baseline visit. However, this decrease had a lesser effect on visual outcomes. The percentage of eyes with poor vision (VA <35 letters) decreased or remained constant in Australia (–0.6%), Spain (–2.1%), and Switzerland (0%), while those with good vision (VA >70 letters) increased in Australia (+1.1%), France (+14.1%), Italy (4.2%), and Spain (+3.7%). These positive outcomes support the clinical decision of deferring DME treatment in favor of nAMD. In RVO, most of the countries decreased the number of injections by 1 (Australia, France, Italy, New Zealand, Spain, and Switzerland) and some by >1 injection (Ireland and Netherlands). The impact on visual outcomes was more variable (from –6.5 to +4.2 letters), probably related to the smaller size of the study cohorts and individual case selection in each center, prioritizing those eyes with neovascular changes or risk of progression to rubeosis.[2]

In summary, this study provides estimates on disruptions to intravitreal therapy and the effect on clinical outcomes caused by the COVID-19 pandemic in an international cohort of eyes. Eyes with nAMD generally lost vision in all countries analyzed in proportion to the reduction in number of injections received during the lockdown. Eyes with DME and RVO were less obviously affected by the reduction in injection numbers that also occurred. The outcomes data reported in this study may serve clinicians to prepare strategies to mitigate vision loss in future pandemics. It appears appropriate to prioritize intravitreal therapy for eyes with nAMD in this scenario.

References

1. Zhu N, Zhang D, Wang W, et al. A novel coronavirus from patients with pneumonia in China. *N Engl J Med*. 2020; 382:727-733.
2. Korobelnik J-F, Loewenstein A, Eldem B, et al. Guidance for anti-VEGF intravitreal injections during the COVID-19 pandemic. *Graefes Arch Clin Exp Ophthalmol*. 2020; 258:1149-1156.
3. Gegúndez-Fernández J, Zarranz-Ventura J, Garay-Aramburu G, et al. Recommendations for eye care during the alarm state by the coronavirus disease pandemic COVID-19. *Arch Soc Esp Oftalmol (English ed.)*. 2020; 95:300-310.
4. Gillies MC, Walton R, Liong J, et al. Efficient capture of high-quality data on outcomes of treatment for macular diseases: the Fight Retinal Blindness! project. *Retina* 2014; 34:188-195.

Developing a Pancoronavirus Vaccine

Lbachir Benmohamed PhD

NOTES

What the Retina Specialist Should Know About Activities at the National Eye Institute

Michael F Chiang MD

What is the National Eye Institute?

The National Eye Institute (NEI) has been a world leader in directing and funding eye and vision research since 1968, when Congress and President Lyndon Johnson established it as an independent entity within the National Institutes of Health (NIH) to manage national efforts in vision science. The current annual NEI budget is $835 million. Now in 2021, the NEI is releasing a new Strategic Plan, which outlines our directions and priorities over the next 5 years and is the first NEI Strategic Plan since 2012.

What are key recent NEI-funded accomplishments in retina?

- Ocular gene therapy
- Cell atlas of human retina and retina organoids
- OCT/OCT angiography, including handheld devices for use at bedside
- DRCR Retina Network (eg, Protocol I, Protocol S, Protocol T)

Why do we need a new NEI Strategic Plan and Mission Statement?

- Unprecedented advances in science and computing have occurred during the past several decades → unique opportunities to improve understanding of disease mechanisms, leading to novel diagnostic and therapeutic tools.
- The COVID-19 pandemic demonstrated the value of investment in research, yet exposed many underlying health disparities and highlighted the importance of making scientific advances accessible to the entire population.
- The revised NEI Mission Statement (first revision since 1968) begins: "The mission of the National Eye Institute is to eliminate vision loss and improve quality of life through vision research."

How is the new NEI Strategic Plan organized to promote collaboration across fields?

- NEI core research programs are currently organized by anatomy and disease (retina; cornea; lens; glaucoma & optic neuropathy; strabismus, amblyopia, visual processing; low vision).
- NEI Strategic Plan is organized around 7 cross-cutting areas of emphasis: genetics, neuroscience, immunology, regenerative medicine, data science, quality of life, and public health & disparities.
- Examples of potential innovations in each area of emphasis

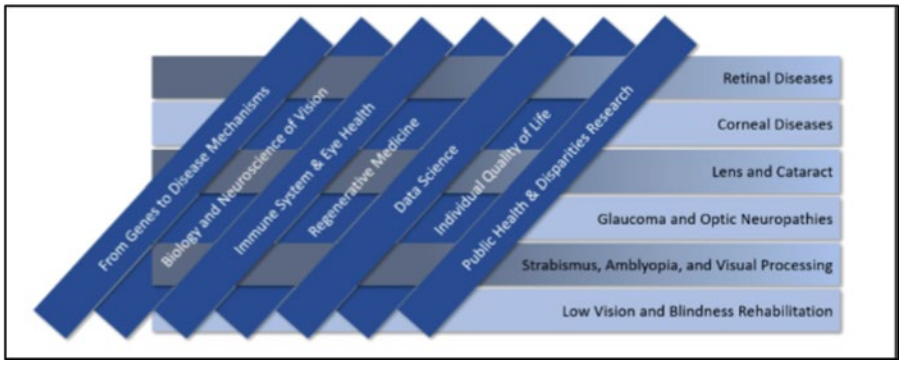


Figure 1. Seven cross-cutting areas of emphasis in National Eye Institute Strategic Plan. These do not replace the existing core program structure but rather highlight evolving areas that will require interdisciplinary approaches.

Current Status of U.S. Fellowship Monitoring and Compliance

Justin Gottlieb MD

I. Introduction
   A. Vitreoretinal fellowships are essentially apprenticeships without a certification board.
   B. Fellowship directors are responsible for the determination of competence of fellows to begin independent practice.

II. Mechanisms of Oversight and Training Guidance of Fellowships
   A. No singular, formally defined and universally accepted structure of oversight in the United States
   B. Association of University Professors in Ophthalmology – Fellowship Compliance Committee (AUPO-FCC)
      1. Training standards for vitreoretinal surgery and medical retina fellowships
      2. Standards established and updated with support of Retina Society, Macula Society, American Society of Retina Specialists
      3. Voluntary participation of fellowship programs
      4. Compliant programs monitored through exit surveys of graduating fellows
      5. No direct assessment of competence of graduating fellows
   C. American Society of Retina Specialists (ASRS)
      1. Largest organization of retina specialists in the world; national advocate for retina subspecialty
      2. Provides valuable education resources for fellowship education—reading lists, virtual lectures, journal clubs, ASRS Grand Rounds
      3. Developing assessment tools to assist fellowship directors in the assessment of fellow progress in training
      4. Fellows-in-training (FIT) complete an activity log during fellowship to allow promotion from FIT to full membership in ASRS. Completion of a retina fellowship is requirement of membership in ASRS.
      5. Fellowship directors may self-identify on behalf of their fellowship program to join the Fellowship Directors Committee.
      6. No direct assessment of fellowships or fellow competence
   D. San Francisco Match
      1. Organizational unit through which most fellows match with fellowships in the United States
      2. Fellowships are not required to participate in the SF Match.
      3. Highlights programs that are compliant with the AUPO-FCC

III. Challenges
   A. Lack of universal training requirements and guidelines
   B. Despite training guidelines/standards established by AUPO-FCC and supported by the ASRS, Macula Society, and Retina Society, no mechanism of direct assessment or enforcement
   C. No requirement of fellowship programs to participate; currently 60% of programs in SF Match voluntarily participate in AUPO-FCC.
   D. No central mechanism for assessment of competence
   E. How do we establish who is a retina specialist in the United States?

The Process of Quality

Quality Standards in Ophthalmology: PPP and OTA

Timothy W Olsen MD

Ophthalmologists are fortunate to have support from many volunteer ophthalmologists at the American Academy of Ophthalmology (the Academy) who help determine current, evidence-based practice quality standards, readily available on the Academy website. This presentation will inform you about how this process evolves, where to find the current guidelines, and what these guidelines mean to your practice and patient care.

First, the published documents that help clarify our quality standards can be found at the Academy website, *Clinical Education* and *Guidelines* (https://www.aao.org/clinical-education).

In this discussion, we will focus on two key documents: the Preferred Practice Pattern® Guidelines (PPP) and the Ophthalmic Technology Assessment (OTA). While there are many other documents from the Quality Office, such as policy statements, compendium, patient safety statements, etc., this talk will focus on the PPP and OTA process.

The PPP and OTA documents are constructed by practicing ophthalmologists from each subspecialty discipline within a specific topic area using three principles: (1) to create clinically relevant documents useful to practitioners, (2) to assign a quality rating of importance to the recommended care process, and (3) to base ratings on the available literature and strength of evidence available.

The PPP documents may not apply to every patient seen, nor are they medical standards to be adhered to in every situation; care must be individualized. However, the PPP documents are designed to help the clinician and are constructed in an environment that reduces conflicts and bias. The OTA documents evaluate new technologies and analyze how the current evidence supports their role and use in clinical practice.

Each document begins with a Cochrane review. Cochrane is an international organization, free of industry support, that provides systematic literature reviews. Cochrane Reviews contain high-quality, up-to-date information to identify and synthesize empirical evidence that meets prespecified eligibility criteria to inform health-care decisions.

The Scottish Intercollegiate Guidelines Network (SIGN) is a systematic method for reviewing the evidence derived from the Cochrane review. An evidence table is then generated, based on the strength of the evidence-base and on the strength of study methodology. Higher to lower document rankings are as follows: (1) meta-analysis and systematic reviews, (2) randomized, controlled clinical trials, (3) observational studies (each associated with a quality rating), (4) nonanalytic studies, and (5) expert opinion (the lowest quality rating). An evidence table is generated, analyzed by a group of practicing physicians, and prioritized based upon the evidence as it applies to clinical practice. Any group member with a financial conflict on a specific topic recuses themselves from any final recommendations, thus reducing bias.

Next, the Grading of Recommendations Assessment Development and Evaluation (GRADE) is applied to determine the strength of the recommendation, balancing between the proposed therapy and the associated risk, and the value proposition in the setting of our health-care environment (see principles of the Hoskins Center for Quality Eye Care). The GRADE also looks at the stability of the data. For example, (1) *Good* quality: Further research is unlikely to change our confidence in the estimated effect, (2) *Moderate* quality: Further research is likely to have an impact, or (3) *Insufficient* quality: Further research is very likely to impact the recommendations. Finally, a group judgment is issued based upon SIGN, GRADE, and final analysis of the topic by weighing the evidence-based data against the risks, undesirable effects, or a balance between options.

All final documents are reviewed and must be approved by the Academy's Board of Trustees. Once published, these documents are carefully considered by providers and by professions outside of ophthalmology. For example, insurance companies and legal professionals refer to these documents regularly and make decisions based upon them. Care is taken during the preparation of these documents to avoid placing ophthalmologists at undue medical-legal risk, emphasizing that patient care must be individualized.

Some limitations of the current PPP and OTA process:

1. The process is time-consuming for volunteers who review the literature.
2. Documents take time to prepare and approve.
3. Thus, there may be a delay between newly published data and inclusion.
4. Documents are expensive to prepare.
5. PPPs and OTAs are used internationally, yet economic situations may limit their applicability, particularly if there are value-based decisions that differ substantially from circumstances in the United States.

In ophthalmology, we are fortunate to have practice guidelines from the Academy that help us assess the published evidence-based literature. Also, newer technologies are assessed using both a weighted, methodologic review and a clinical analysis from our practicing colleagues, to help us better incorporate these technologies into our practices.

Diversity, Equity, and Inclusion in Retina

Julia A Haller MD

Resources

With acknowledgment to H Gill , R L Niederer , E Shriver, L K Gordon, A L Coleman, H V Danesh-Meyer. An eye on gender equity: a review of the evolving role and representation of women in ophthalmology. *Am J Ophthalmol*. 2021; S0002-9394(21)00372-X.

1. Tsui I. The glass ceiling in ophthalmology—next comes how to change this. *JAMA Ophthalmol*. 2019; 137(11):1231-1232.
2. The Lancet. *Feminism is for everybody*. *Lancet*. 2019; 393(10171):493.
3. AAMC. Diversity in medicine: facts and figures 2019. Available from: https://www.aamc.org/data-reports/workforce/report/diversity-medicine-facts-and-figures-2019.
4. Lo TCS, Rogers SL, Hall AJ, Lim LL. Differences in practice of ophthalmology by gender in Australia. *Clin Exp Ophthalmol*. 2019; 47(7):840-846.
5. Kuhlmann E, Ovseiko PV, Kurmeyer C, et al. Closing the gender leadership gap: a multi-centre cross-country comparison of women in management and leadership in academic health centres in the European Union. *Hum Resour Health*. 2017; 15(1):2.
6. Mansour AM, Shields CL, Maalouf FC, et al. Five-decade profile of women in leadership positions at ophthalmic publications. *Arch Ophthalmol*. 2012; 130(11):1441-1446.
7. Reddy AK, Bounds GW, Bakri SJ, et al. Representation of women with industry ties in ophthalmology. *JAMA Ophthalmol*. 2016; 134(6):636-643.
8. Xierali IM, Nivet MA, Wilson MR. Current and future status of diversity in ophthalmologist workforce. *JAMA Ophthalmol*. 2016; 134(9):1016-1023.
9. Kramer PW, Kohnen T, Groneberg DA, Bendels MHK. Sex disparities in ophthalmic research: a descriptive bibliometric study on scientific authorships. *JAMA Ophthalmol*. 2019; 137(11):1223-1231.
10. Royal College of Ophthalmologists. Workforce Census 2016. Available from: https://www.rcophth.ac.uk/wp-content/uploads/2017/03/RCOphth-Workforce-Census-2016.pdf.
11. Association of American Medical Colleges. Active physicians by sex and specialty, 2019. Available from: https://www.aamc.org/data-reports/workforce/interactive-data/active-physicians-sex-and-specialty-2019.
12. Weiss A, Lee KC, Tapia V, et al. Equity in surgical leadership for women: more work to do. *Am J Surg*. 2014; 208(3):494-498.
13. Laver KE, Prichard IJ, Cations M, Osenk I, Govin K, Coveney JD. A systematic review of interventions to support the careers of women in academic medicine and other disciplines. *BMJ Open*. 2018; 8(3):e020380.
14. Cruz OA, Johnson NB, Thomas SM. Twenty-five years of leadership: a look at trends in tenure and appointments of chairs of ophthalmology. *Ophthalmology* 2009; 116(4):807-811.
15. Shah DN, Volpe NJ, Abbuhl SB, Pietrobon R, Shah A. Gender characteristics among academic ophthalmology leadership, faculty, and residents: results from a cross-sectional survey. *Ophthalmic Epidemiol*. 2010; 17(1):1-6.
16. Dotan G, Qureshi HM, Saraf SS, Darnley-Fisch DA. Leadership of United States academic departments of ophthalmology: chairperson characteristics, accomplishments, and personal insights. *Am J Ophthalmol*. 2018; 186:69-76.
17. Camacci ML, Lu A, Lehman EB, Scott IU, Bowie E, Pantanelli SM. Association between sex composition and publication productivity of journal editorial and professional society board members in ophthalmology. *JAMA Ophthalmol*. 2020; 138(5):451-458.
18. Nguyen AX, Ratan S, Biyani A, et al. Gender of award recipients in major ophthalmology societies. *Am J Ophthalmol*. 2021; 231:120-133.
19. Lautenberger DMDV, Raezer CL, Sloane RA. The state of women in academic medicine: the pipeline and pathways to leadership, 2018-2019. Available from: https://store.aamc.org/the-state-of-women-in-academic-medicine-2018-2019-exploring-pathways-to-equity.html.
20. Charters L. AAO president paving a leadership path for women in ophthalmology 2020. *Ophthalmology Times*, Oct. 9, 2020. Available from: https://www.ophthalmologytimes.com/view/aao-president-paving-a-leadership-path-for-women-in-ophthalmology.
21. Jain NS, Kersten HM, Watson SL, Danesh-Meyer HV. Gender differences in Australasian ophthalmologists' experiences of the workplace. *Clin Exp Ophthalmol*. 2019; 47(6):706-712.
22. One hundred reasons to celebrate women in ophthalmology. The Ophthalmologist website. 2021. Available from: https://theophthalmologist.com/power-list/2021.
23. Association of American Medical Colleges. Table 4A: Distribution of full-time women M.D. faculty by department and rank, 2015. Available from: https://www.aamc.org/system/files/reports/1/2020table4a.pdf.
24. Franco-Cardenas V, Rosenberg J, Ramirez A, Lin J, Tsui I. Decadelong profile of women in ophthalmic publications. *JAMA Ophthalmol*. 2015; 133(3):255-259. Erratum in: *JAMA Ophthalmol*. 2016; 134(10):1204.
25. Dotan G, Qureshi HM, Gaton DD. Chairs of United States academic ophthalmology departments: a descriptive analysis and trends. *Am J Ophthalmol*. 2018; 196:26-33.
26. Association of American Medical Colleges. U.S. medical school faculty by sex, race/ethnicity, rank, and department, 2020. Available from: https://www.aamc.org/data-reports/faculty-institutions/interactive-data/2020-us-medical-school-faculty.
27. Tuli SS. Status of women in academic ophthalmology. *J Acad Ophthalmol*. 2019; 11:e59-e64.
28. Silva NA, Cerasiello SY, Herendeen JS, et al. Gender differences in NIH grant funding in neurological surgery. *J Clin Neurosci*. 2020; 80:43-49.

29. Witteman HO, Hendricks M, Straus S, Tannenbaum C. Are gender gaps due to evaluations of the applicant or the science? A natural experiment at a national funding agency. *Lancet* 2019; 393(10171):531-540.
30. Rusakevich AM, Protopsaltis NJ, Rao RC, Chao DL, Yiu G. Research funding, income, and career satisfaction among clinician-scientists in ophthalmology in the United States. *Am J Ophthalmol*. 2021; 227:254-264.
31. Chiam M, Camacci ML, Lehman EB, Chen MC, Vora GK, Pantanelli SM. Sex differences in academic rank, scholarly productivity, National Institutes of Health Funding, and industry ties among academic cornea specialists in the United States. *Am J Ophthalmol*. 2021; 222:285-291.
32. Shah DN, Huang J, Ying GS, Pietrobon R, O'Brien JM. Trends in female representation in published ophthalmology literature, 2000-2009. *Digit J Ophthalmol*. 2013; 19(4):50-55.
33. Mimouni M, Zayit-Soudry S, Segal O, et al. Trends in authorship of articles in major ophthalmology journals by gender, 2002-2014. *Ophthalmology* 2016; 123(8):1824-1828.
34. Kalavar M, Watane A, Balaji N, et al. Authorship gender composition in the ophthalmology literature from 2015 to 2019. *Ophthalmology* 2021; 128(4):617-619.
35. Sridhar J, Kuriyan AE, Yonekawa Y, et al. Representation of women in vitreoretinal meeting faculty roles from 2015 through 2019. *Am J Ophthalmol*. 2021; 221:131-136.
36. Zhuge Y, Kaufman J, Simeone DM, Chen H, Velazquez OC. Is there still a glass ceiling for women in academic surgery? *Ann Surg*. 2011; 253(4):637-643.
37. Magua W, Zhu X, Bhattacharya A, et al. Are female applicants disadvantaged in National Institutes of Health peer review? combining algorithmic text mining and qualitative methods to detect evaluative differences in R01 reviewers' critiques. *J Womens Health (Larchmt)*. 2017; 26(5):560-570.
38. Xie Y, Shauman KA. Sex differences in research productivity: new evidence about an old puzzle. *Am Sociol Rev*. 1998; 847-870.
39. Moss-Racusin CA, Dovidio JF, Brescoll VL, Graham MJ, Handelsman J. Science faculty's subtle gender biases favor male students. *Proc Natl Acad Sci U S A*. 2012; 109(41):16474-16479.
40. Jena AB, Olenski AR, Blumenthal DM. Sex differences in physician salary in US public medical schools. *JAMA Intern Med*. 2016; 176(9):1294-1304.
41. Reddy AK, Bounds GW, Bakri SJ, et al. Differences in clinical activity and Medicare payments for female vs male ophthalmologists. *JAMA Ophthalmol*. 2017; 135(3):205-213.
42. Danesh-Meyer HV, Deva NC, Ku JY, Carroll SC, Tan YW, Gamble G. Differences in practice and personal profiles between male and female ophthalmologists. *Clin Exp Ophthalmol*. 2007; 35(4):318-323.
43. Powell S. Mind the gap. *Optometry Today*, April 10, 2018, Available from: https://www.aop.org.uk/ot/industry/high-street/2018/04/10/mind-the-gap.
44. Jia JS, Lazzaro A, Lidder AK, et al. Gender compensation gap for ophthalmologists in the first year of clinical practice. *Ophthalmology* 2021; 128(7):971-980.
45. Peckham C. Medscape Ophthalmologist Compensation Report, 2015. Available from: https://www.medscape.com/features/slideshow/compensation/2015/ophthalmology#page=5.
46. Christmann DL. Women and their role in ophthalmology. 2015. Available from: https://www.wioonline.org/news/women-role-ophthalmology/.
47. Jinapriya D, Cockerill R, Trope GE. Career satisfaction and surgical practice patterns among female ophthalmologists. *Can J Ophthalmol*. 2003; 38(5):373-378. Erratum in: *Can J Ophthalmol*. 2003; 38(7):538.
48. McAlister C, Jin YP, Braga-Mele R, DesMarchais BF, Buys YM. Comparison of lifestyle and practice patterns between male and female Canadian ophthalmologists. *Can J Ophthalmol*. 2014; 49(3):287-290.
49. Rimmer A. The gender pay gap: female doctors still earn a third less than male doctors. *BMJ*. 2017; 357:j196.
50. Grossman RC. The gender pay gap in medicine: causes and solutions. In: *Gender Equity in the Medical Profession*. IGI Global; 2020:110-127.
51. Meyerson SL, Sternbach JM, Zwischenberger JB, Bender EM. The effect of gender on resident autonomy in the operating room. *J Surg Educ*. 2017; 74(6):e111-e118.
52. Haller JA, Zhang Q. A seat at the operating room table in ophthalmology surgery. *JAMA Ophthalmol*. 2019; 137(9):1020-1021.
53. Ali A, Subhi Y, Ringsted C, Konge L. Gender differences in the acquisition of surgical skills: a systematic review. *Surg Endosc*. 2015; 29(11):3065-3073.
54. Gong D, Winn BJ, Beal CJ, et al. Gender differences in case volume among ophthalmology residents. *JAMA Ophthalmol*. 2019; 137(9):1015-1020.
55. Gibson A, Boulton MG, Watson MP, Moseley MJ, Murray PI, Fielder AR. The first cut is the deepest: basic surgical training in ophthalmology. *Eye (Lond)*. 2005; 19(12):1264-1270.
56. Fnais N, Soobiah C, Chen MH, et al. Harassment and discrimination in medical training: a systematic review and meta-analysis. *Acad Med*. 2014; 89(5):817-827.
57. The Lancet. Besting bullying. *Lancet* 2020; 395(10227):840.
58. Crebbin W, Campbell G, Hillis DA, Watters DA. Prevalence of bullying, discrimination and sexual harassment in surgery in Australasia. *ANZ J Surg*. 2015; 85(12):905-909.
59. Jain NS, Gill HK, Kersten HM, Watson SL, Danesh-Meyer H. Bullying and harassment in ophthalmology: a trainee survey. *N Z Med J*. 2020; 133(1512):102-103.
60 Meyer JA, Troutbeck R, Oliver GF, Gordon LK, Danesh-Meyer HV. Bullying, harassment and sexual discrimination among ophthalmologists in Australia and New Zealand. *Clin Exp Ophthalmol*. 2021; 49(1):15-24.
61. The Lancet. Time's up for sexual harassment in medicine. *Lancet* 2018; 391(10140):2576.
62. Hinze SW. 'Am I being over-sensitive?' Women's experience of sexual harassment during medical training. *Health (London)*. 2004; 8(1):101-127.
63. Hu YY, Ellis RJ, Hewitt DB, et al. Discrimination, abuse, harassment, and burnout in surgical residency training. *N Engl J Med*. 2019; 381(18):1741-1752.
64. Scruggs BA, Hock LE, Cabrera MT, et al. A U.S. survey of sexual harassment in ophthalmology training using a novel standardized scale. *J Acad Ophthalmol*. 2020; 12(1):e27-e35.
65. Hock LE, Scruggs BA, Barlow PB, Oetting TA, Abràmoff MD, Shriver EM. Responding to patient-initiated verbal sexual harassment: outcomes of a pilot training for ophthalmologists. *J Acad Ophthalmol*. 2020; 12(2):e175-e180.

66. AlShebli B, Makovi K, Rahwan T. Retraction note: The association between early career informal mentorship in academic collaborations and junior author performance. *Nat Commun*. 2020; 11(1):6446.

67. Regarding mentorship. *Nat Commun*. 2020; 11:6447.

68. Bickel J. How men can excel as mentors of women. *Acad Med*. 2014; 89(8):1100-1102.

69. Men, women and work. The gender pay gap. Women still earn a lot less than men, despite decades of equal pay laws. Why? *The Economist*, Oct. 7, 2017. Available from: https://www.economist.com/international/2017/10/07/the-gender-pay-gap.

70. Fried LP, Francomano CA, MacDonald SM, et al. Career development for women in academic medicine: multiple interventions in a department of medicine. *JAMA*. 1996; 276(11):898-905.

71. Kang SK, Kaplan S. Working toward gender diversity and inclusion in medicine: myths and solutions. *Lancet* 2019; 393(10171):579-586.

72. Coe IR, Wiley R, Bekker LG. Organisational best practices towards gender equality in science and medicine. *Lancet* 2019; 393(10171):587-593.

73. Castilla EJ, Benard S. The paradox of meritocracy in organizations. *Adm Sci Q*. 2010; 55:543-676.

74. AMA. AMA Gender Equity Summit Report 2019. Available from: https://ama.com.au/articles/ama-gender-equity-summit-report-2019.

Variations in Vitreoretinal Physician Utilization of Ancillary Testing: An IRIS® Registry Analysis

Theodore Leng MD

Introduction

With over 367 million patient visits from 66 million unique patients, the American Academy of Ophthalmology's IRIS® (Intelligent Research in Sight) Registry is representative of the practice of ophthalmology in the United States. This presentation will elucidate variations in vitreoretinal physician utilization of ancillary testing, stratified by factors.

We hypothesized that practice patterns of vitreoretinal physicians could vary across location, practice size, payer mix, clinical and surgical volume, diagnostic distribution, and EHR type, among other factors. This study analyzed the real-world data in the IRIS® Registry to explore these differences.

Methods

Observational study using the IRIS® Registry to identify the OCT, intravenous fluorescein angiography (FA), and color fundus photograph (CFP) usage patterns of vitreoretinal physicians between January 1, 2018, and December 31, 2020. Monthly counts of OCTs, FAs, and CFPs were attributed to retinal practitioners and stratified according to geographic location, practice volume (based on number of patient visits per month), diagnostic diversity (based on proportion of AMD patients), surgical volume, payer mix (Medicare/Medicaid ratio), practice type (academic vs. nonacademic), EHR type, and number of new neovascular AMD patients per year.

Results and Conclusions

The results revealed variations in practice patterns of vitreoretinal specialists in the United States, which can have several influencing factors. Further exploration of these variances could lead to optimization of ancillary testing recommendations to improve patient outcomes and the overall cost of care in retina.

In These Unprecedented Times . . .

2021 Retina Subspecialty Day

Gareth M Lema MD PhD

The COVID-19 pandemic has impacted us in many ways, including our ability to effectively raise critical funds used to protect sight and empower lives. This objective requires active participation and commitment to advocacy from every ophthalmologist. Contributions to the following three critical funds are a part of that commitment:

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

During AAO 2021 in New Orleans, invest in OPHTHPAC and Surgical Scope Fund at one of our two booths in the convention center or online. You may also invest via phone by texting MDEYE to 41444 for OPHTHPAC and SCOPE to 51555 for the Surgical Scope Fund.

We also encourage you to stop by our booth in the Hall B Lobby to learn more about OPHTHPAC Direct, a unique program that lets you decide who receives your political support.

Please help us in these unprecedented times to continue to protect quality patient eye care for everybody. Two Academy committees made up of your ophthalmology colleagues are working hard on your behalf to ensure this outcome. The OPHTHPAC Committee continues to identify Congressional Advocates in each state to maintain close relationships with federal legislators to advance ophthalmology and patient causes. The Surgical Scope Fund Committee is raising funds to be used to protect Surgery by Surgeons during scope battles at the state level.

Our mission of "protecting sight and empowering lives" requires robust funding of both OPHTHPAC and the Surgical Scope Fund. Each of us has a responsibility to ensure that these funds are strong so that ophthalmology continues to strive, especially in these unprecedented times.

OPHTHPAC®

OPHTHPAC represents the profession of ophthalmology to the U.S. Congress. OPHTHPAC's most recent victories include the following:

Physician Relief

- ✓ Securing access to COVID-19 relief, including Provider Relief Funds and forgivable small business loans
- ✓ Pushing Congress to enact a provider-friendly "surprise" medical billing law

Medicare Payment

- ✓ Mitigating drastic Medicare cuts
- ✓ Obtaining a one-year moratorium extension on the 2% Medicare budget sequestration cut

Research & Relationships

- ✓ Increasing vision research funding by $11.6 million
- ✓ Helping get three new physicians elected to Congress, including an ophthalmologist

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

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

Get engaged with OPHTHPAC and help strengthen ophthalmology's voice on Capitol Hill as we address the following legislative and regulatory issues this year:

- Improving Medicare physician payments
- Fighting optometric scope expansion in the Veterans' Health Administration
- Obtaining relief from prior authorization and step therapy requirements that delay patient care
- Seeking solutions for rising drug prices and access to drugs in shortage
- Ensuring fair reimbursements for Part B drugs

At the Academy's annual Congressional Advocacy Day, the Academy and the **American Society of Retina Specialists (ASRS)**, the **Macula Society**, and the **Retina Society** ensure a strong presence of retina specialists to support ophthalmology's priorities. These three societies also supports participation of young ophthalmologists via the Academy's Advocacy Ambassador Program. Ophthalmologists visit members of Congress and their key health staff to discuss ophthalmology priorities as part of Congressional Advocacy Day. The three retina societies remain a crucial partners with the Academy in its ongoing federal and state advocacy initiatives.

Surgical Scope Fund (SSF)

The Surgical Scope Fund (SSF) provides grants to state ophthalmology societies to support their efforts to protect patient safety from dangerous optometric surgery proposals. Since its inception, the Surgery by Surgeons campaign and the SSF, in partnership with state ophthalmology societies, has helped 41 state/territorial ophthalmology societies reject optometric scope-of-practice expansions into surgery.

If you already have made a SSF contribution, please go to safesurgerycoalition.org to see the impact of your gift.

Dollars from the SSF are critical to building complete, cutting-edge political campaigns, including media efforts (TV, radio, and social media), educating and building relationships with legislators, and educating the voting public to contact their legislators. These political campaigns help the SSF to protect patient safety by defeating optometry's surgical initiatives.

Each of these endeavors is very expensive, and no one state has the critical resources to battle big optometry on their own.

Ophthalmologists must join together and donate to the SSF and to fight for patient safety.

The Secretariat for State Affairs thanks the American Society of Retina Specialists (ASRS), the Macula Society, and the Retina Society, who have joined state ophthalmology societies in the past in contributing to the SSF, and looks forward to their 2021 contributions. These ophthalmic organizations complete the necessary SSF support structure for the protection of our patients' sight.

State Eye PAC

It is increasingly important for all ophthalmologists to support their respective State Eye PACs because campaign contributions to legislators at the state level must come from individual ophthalmologists and cannot come from the Academy, OPHTHPAC, or the Surgical Scope Fund. 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: Support ophthalmology's advocacy efforts

Academy Surgical Scope Fund 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. Surgical Scope Fund contributions are completely confidential and may be made with corporate checks or credit cards. PAC contributions may be 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 that ensures ophthalmology has a strong voice in advocating for patients.

OPHTHPAC Committee

Jeffrey S Maltzman, MD (AZ)—Chair
Janet A Betchkal, MD (FL)
Mark J Gallardo MD (TX)
Thomas A Graul MD (NE)
Sohail J Hasan MD PhD (IL)
S Anna Kao MD (GA)
Julie S Lee MD (KY)
Stephanie J Marioneaux MD (VA)
Dorothy M Moore MD (DE)
Stephen H Orr MD (OH)
Niraj Patel MD (WA)
Michelle K Rhee MD (NY)
Linda Schumacher-Feero MD (ME)
Frank A Scotti MD (CA)
Jeffrianne S Young MD (IA)

Ex-Officio Members:

Tamara R Fountain MD (IL)
David B Glasser MD (MD)
David W Parke II MD (CA)
Michael X Repka MD MBA (MD)
George A Williams MD (MI)

Surgical Scope Fund Committee

Lee A Snyder MD (MD)—Chair
Vineet ("Nick") Batra MD (CA)
Robert L Bergren MD (PA)
Gareth M Lema MD PhD (NY)
Darby D Miller MD MPH (FL)
Amalia Miranda MD (OK)
Christopher C Teng MD (CT)

Ex-Officio Members:

John D Peters MD (NE)
George A Williams MD (MI)

Surgical Scope Fund	OPHTHPAC®	State EyePAC
To protect patient safety by defeating optometric surgical scope-of-practice initiatives that threaten quality surgical care	Working across the political spectrum to advance ophthalmology and protect its members and patients at the federal level. Support for candidates for U.S. Congress.	Support for candidates for state House, Senate, and governor
Political grassroots activities, government relations, PR and media campaigns	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, corporate, and organization	Personal and corporate contributions are accepted.	
Contributions are 100% confidential.	Contributions $200 and above are on the public record.	Contributions are on the public record depending upon state statutes.

Advanced Retinal Implants

Mark S Humayun MD PhD

I. Bioelectronic Implants
   A. Nonbioelectronic ophthalmic implants (briefly)
   B. Bioelectronic retinal implants
      1. Unmet medical need
      2. Target patient population
      3. Feasibility studies
      4. Human studies
      5. Future direction
   C. Bioelectronic visual cortical implants (briefly)

II. Stem Cell Implants
   A. Unmet medical need
   B. Target patient population
   C. Feasibility studies
   D. Human studies
   E. Future direction

III. Conclusions

My Best Medical Retina Case

Moderator: William F Mieler MD

Amani Fawzi MD, Lee M Jampol MD, J Michael Jumper MD, David Sarraf MD

NOTES

Should We Reconsider the Diagnosis of Idiopathic Uveal Effusion Syndrome?

Alain Gaudric MD

The pathogenesis of idiopathic uveal effusion syndrome is unclear, and its diagnostic should be retained only after eliminating other causes of exudative retinal detachment associated with choroidal detachment. One of the main differential diagnoses is central serous chorioretinopathy (CSCR) with bullous inferior retinal detachment that everything seems to oppose. In fact, both conditions might have more links together than previously thought.

1. Idiopathic Uveal Effusion Syndrome (IUES)

IUES is a rare disease characterized by the association of an annular ciliochoroidal detachment and an inferior retinal detachment, typically shifting with the patient's position. It was first described by Schepens and Brockhurst[1] as a uveal effusion in 1963.[2] Later, the term "IUES" has been used to differentiate this condition from nanophthalmic UE. Only a few multimodal images of IUES are available in the literature.

IUES is thought to be due to a scleral thickening or an abnormal scleral structure that could lead to choroidal thickening through different mechanisms.

First, the scleral thickening and stiffness could narrow the transscleral passage of the vortex veins, impairing the venous outflow and leading to choroidal congestion, as proposed by Gass.[3]

A second hypothesis is that the abnormal scleral thickness and structure could impede the normal flow of transscleral fluid through the sclera,[4,5] resulting in the accumulation of proteins in the suprachoroidal space and increasing fluid collection through an oncotic mechanism.[2]

Secondary causes of UE should be considered and investigated such as medication, orbital mass, lymphoma, multiple myeloma, Vogt-Koyanagi-Harada disease and other chronic uveitis, posterior scleritis (review by Elagouz M et al[6]), and bilateral diffuse uveal melanocytic proliferation.[7] However, the differential diagnosis with some cases of CSCR is not always easy.

2. Central Serous Chorioretinopathy (CSCR)

CSCR with inferior bullous retinal detachment was first described by Gass in 1973,[8] and another series of 21 cases analyzed with multimodal imaging has been reported in 2016 by Balaratnasingam et al,[9] who have reported the frequency of retinal pigment epithelium tears, retinal folds, and subretinal fibrin but the absence of ciliochoroidal detachment.

CSCR publications have also suggested that the choroidal vein dilation initially seen in indocyanine green angiography (ICGA) by Prunte and Flammer in 1996[10] could be due to an engorged vortex vein ampulla as seen in UES.[11,12] An impaired choroidal venous drainage[11] could explain the dilation of the choroidal veins seen on ICGA[13-15] and the choroidal hyperfluorescence seen during the mid-phase of ICGA.[16,17]

It is also noteworthy that the scleral thickness measured in the anterior segment of CSCR eyes is greater than in control eyes, as recently reported.[18]

Lastly, it has been shown that CSCR occurs in emmetropic or moderately hypermetropic eyes, but not in myopic eyes.[19] This is also the case for IUES, and our cases had an axial length ranging between 21.1 and 23.9 mm. This observation supports a potentially thick sclera in such cases.

3. CSCR with Inferior Bullous Retinal Detachment and Choroidal Detachment

We have observed 4 eyes from 3 patients who had a history of CSCR or presented with signs of CSCR in the fellow eye and shared with IUES the presence of an annular ciliochoroidal detachment associated with an inferior non-rhegmatogenous retinal detachment.[20] However, they showed defined subretinal leaking points above the limits of the inferior bullous retinal detachment, while no fluorescein leakage has been reported in IUES.[15,16]

Our cases had axial lengths ranging between 21.1 and 23.9 mm, ruling out the diagnosis of nanophthalmos.

Also, as in IUES, our cases showed a "leopard-spot" appearance of the fundus, characterized by a mottling hyperpigmentation at the retinal pigment epithelium,[16,21] while "leopard spots" have also been reported in severe CSCR.[22]

Our cases had the particularity of presenting the aspect of a bullous variant of CSCR but associated with an annular ciliochoroidal detachment that is specific to IUES. To our knowledge, only 1 case showing some similarities with our cases has been reported, but no OCT image and no image of the periphery were shown, and the authors have concluded that nonspecific choroidal inflammation could be responsible for IUES.[14] Two other publications have reported a choroidal thickening in IUES,[13,15] suggesting that IUES could be part of the pachychoroid spectrum diseases.[15,17]

While the cause of pachychoroid in CSCR has not yet been elucidated, an exudation through choriocapillaris units in areas of dilated choroidal veins has often been suggested to explain the choroidal thickening.[17,23,24] The fact than photodynamic therapy targeted on choroidal plaques of hyperpermeability results in reduction of choroidal thickness reinforces this hypothesis.[25,26] The loculation of the suprachoroidal fluid that has been shown at the posterior pole in some CSCR cases[24] could be due to the excess of fluid extravasation in the choroid. The role of choroidal vein stasis[17] in choriocapillaris hyperpermeability and choroid thickening has also been questioned, as well as the relationship between CSCR and IUES.[11]

We were not able to definitively explain these cases of CSCR presenting as IUES, but they could correspond to transitional forms between the diseases that could have in common a short axial length, a scleral thickening, and choroidal venous congestion. The absence of fluorescein leakage in angiography is therefore important to retain the diagnosis of IEUS.

The management of this rare but severe retinal disease should include systematic medical and biological workup, orbital imaging, and a close follow-up. With proper diagnosis of CSCR in these cases, unnecessary or deleterious corticosteroid treatment can be avoided. However, partial posterior sclerectomies may be an effective treatment, as in IUES.

References

1. Schepens CL, Brockhurst RJ. Uveal effusion: 1. Clinical picture. *Arch Ophthalmol.* 1963; 70:189-201.
2. Gass JD, Jallow S. Idiopathic serous detachment of the choroid, ciliary body, and retina (uveal effusion syndrome). *Ophthalmology* 1982; 89:1018-1032.
3. Gass JD. Uveal effusion syndrome. a new hypothesis concerning pathogenesis and technique of surgical treatment. *Retina* 1983; 3:159-163.
4. Bill A. Movement of albumin and dextran through the sclera. *Arch Ophthalmol.* 1965; 74:248-252.
5. Forrester JV, Lee WR, Kerr PR, Dua HS. The uveal effusion syndrome and trans-scleral flow. *Eye (Lond).* 1990; 4(pt 2):354-365.
6. Elagouz M, Stanescu-Segall D, Jackson TL. Uveal effusion syndrome. *Surv Ophthalmol.* 2010; 55:134-145.
7. Jabbarpoor Bonyadi MH, Ownagh V, Rahimy E, Soheilian M. Giraffe or leopard spot chorioretinopathy as an outstanding finding: case report and literature review. *Int Ophthalmol.* 2019; 39:1405-1412.
8. Gass JD. Bullous retinal detachment. an unusual manifestation of idiopathic central serous choroidopathy. *Am J Ophthalmol.* 1973; 75:810-821.
9. Balaratnasingam C, Freund KB, Tan Am, et al. Bullous variant of central serous chorioretinopathy: expansion of phenotypic features using multimethod imaging. *Ophthalmology* 2016; 123:1541-1552.
10. Prünte C, Flammer J. Choroidal capillary and venous congestion in central serous chorioretinopathy. *Am J Ophthalmol.* 1996; 121:26-34.
11. Hiroe T, Kishi S. Dilatation of asymmetric vortex vein in central serous chorioretinopathy. *Ophthalmol Retin.* 2018; 2:152-161.
12. Pang CE, Shah VP, Sarraf D, Freund KB. Ultra-widefield imaging with autofluorescence and indocyanine green angiography in central serous chorioretinopathy. *Am J Ophthalmol.* 2014; 158:362-371.E362.
13. Harada T, Machida S, Fujiwara T, et al. Choroidal findings in idiopathic uveal effusion syndrome. *Clin Ophthalmol.* 2011; 5:1599-1601.
14. Kumar A, Kedar S, Singh RP. The indocyanine green findings in idiopathic uveal effusion syndrome. *Indian J Ophthalmol.* 2002; 50:217-219.
15. Terubayashi Y, Morishita S, Kohmoto R, et al. Type III uveal effusion syndrome suspected to be related to pachychoroid spectrum disease: a case report. *Medicine (Baltimore)* 2020; 99:E21441.
16. Uyama M, Takahashi K, Kozaki J, et al. Uveal effusion syndrome: clinical features, surgical treatment, histologic examination of the sclera, and pathophysiology. *Ophthalmology* 2000; 107:441-449.
17. Spaide RF, Cheung CMG, Matsumoto H, et al. Venous overload choroidopathy: a hypothetical framework for central serous chorioretinopathy and allied disorders. *Prog Retin Eye Res.* Epub ahead of print 2021 May 21; 100973.
18. Imanaga N, Terao N, Nakamine S, et al. Scleral thickness in central serous chorioretinopathy. *Ophthalmol Retin.* 2021; 5(3):285-291.
19. Terao N, Koizumi H, Kojima K, et al. Short axial length and hyperopic refractive error are risk factors of central serous chorioretinopathy. *Br J Ophthalmol.* 2020; 104:1260-1265.
20. Boulanger E, Bonnin S, Delahaye-Mazza C, et al. Central serous chorioretinopathy mimicking idiopathic uveal effusion syndrome. *Retin Cases Brief Rep.* Epub ahead of print 2021 Jun 1. doi: 10.1097/ICB.0000000000001170.
21. Green WR, Kincaid MC, Fogle JA. Uveal effusion syndrome. *Trans Ophthalmol Soc U K.* 1981; 101 (pt 3):368-375.
22. Iida T, Spaide RF, Haas A, et al. Leopard-spot pattern of yellowish subretinal deposits in central serous chorioretinopathy. *Arch Ophthalmol.* 2002; 120:37-42.
23. Imamura Y, Fujiwara T, Margolis R, Spaide RF. Enhanced depth imaging optical coherence tomography of the choroid in central serous chorioretinopathy. *Retina* 2009; 29:1469-1473.
24. Spaide RF, Ryan EH. Loculation of fluid in the posterior choroid in eyes with central serous chorioretinopathy. *Am J Ophthalmol.* 2015; 160:1211-1216.
25. Razavi S, Souied EH, Cavallero E, et al. Assessment of choroidal topographic changes by swept source optical coherence tomography after photodynamic therapy for central serous chorioretinopathy. *Am J Ophthalmol.* 2014; 157:852-860.
26. Maruko I, Iida T, Sugano Y, et al. Subfoveal choroidal thickness after treatment of central serous chorioretinopathy. *Ophthalmology* 2010; 117:1792-1799.

Central Serous Chorioretinopathy: What Can We Learn From OCT Angiography?

Nicole Eter MD

I. Classification of Central Serous Chorioretinopathy (CSC)
   A. Acute/chronic
   B. Simple/complex/atypical
   C. Primary/recurrent/resolved/persistent
   D. CSC with macular neovascularization

II. Multimodal Imaging
   A. Fluorescein angiography
   B. Indocyanine green angiography
   C. Fundus autofluorescence
   D. Near infrared imaging
   E. OCT
   F. OCT angiography

III. OCT Angiographic Features in CCS
   A. Impaired choriocapillaris blood flow
   B. Impaired retinal circulation and foveal avascular zone
   C. Focal choroidal excavation
   D. Macular neovascularization
   E. Fellow eye

IV. Treatment
   A. Await spontaneous
   B. Pharmacological therapy
   C. Laser options
   D. Photodynamic therapy

Selected Readings

1. Nelis P, Clemens CR, Alten F, Eter N. OCT angiography reveals changes in foveal vessel architecture and foveal flow in central serous chorioretinopathy. *Acta Ophthalmol.* 2017; 95(8):e802-e803.
2. Golshahi A, Klingmüller D, Holz FG, Eter N. Ketoconazole in the treatment of central serous chorioretinopathy: a pilot study. *Acta Ophthalmol.* 2010; 88(5):576-581.
3. Conrad R, Weber NF, Lehnert M, Holz FG, Liedtke R, Eter N. Alexithymia and emotional distress in patients with central serous chorioretinopathy. *Psychosomatics* 2007; 48(6):489-495.
4. Chablani J, Cohen FB; Central Serous Chorioretinopathy International Group. Multimodal imaging-based central serous chorioretinopathy classification. *Ophthalmol Retina*. 2020; 4(11):1043-1046.
5. Arora S, Kulikov AN, Maltsev DS. Implementation of the new multimodal imaging-based classification of central serous chorioretinopathy. *Eur J Ophthalmol.* Epub ahead of print 2021 May 4. doi: 10.1177/11206721211013651.
6. Kaye R, Chandra S, Sheth J, Boon CJF, Sivaprasad S, Lotery A. Central serous chorioretinopathy: an update on risk factors, pathophysiology and imaging modalities. *Prog Retin Eye Res*. Epub ahead of print 2020 Nov. doi: 10.1016/j.preteyeres.2020.100865.
7. Liu J, Chen C, Li L, Xu Y, Yi Z, He L, Zheng H. Assessment of choriocapillary blood flow changes in response to half-dose photodynamic therapy in chronic central serous chorioretinopathy using optical coherence tomography angiography. *BMC Ophthalmol.* 2020; 20(1):402.
8. Vilela M, Mengue C. Central serous chorioretinopathy classification. *Pharmaceuticals* 2020; 14(1):26.
9. Bloom SM, Singal IP. Revised classification of the optical coherence tomography outer retinal bands based on central serous chorioretinopathy analysis. *Retina* 2021; 41(1):181-188.
10. Gupta A, Tripathy K. Central serous chorioretinopathy. In: StatPearls [Internet]. 2021 Feb 14. PMID: 32644399.
11. Sing SR, Matet A, von Dijk EHC, et al. Discrepancy in current central serous chorioretinopathy classification. *Br J Ophthalmol.* 2019; 103:737-742.
12. Venkatesh R, Agarwal SK, Bavaharan B, et al. Multicolour imaging in central serous chorioretinopathy. *Clin Exp Optom*. 2020; 103:324-331.
13. Nkrumah G, Paez-Escamilla M, Singh SR, Rasheed MA, Maltsev D, Guduru A, Chhablani J. Biomarkers for central serous chorioretinopathy. *Ther Adv Ophthalmol.* 2020; 12:1-14.
14. Chronopoulos A, Kakkassery V, Strobel MA, Fornoff L, Hattenbach LO. The significance of pigment epithelial detachment in central serous chorioretinopathy. *Eur J Ophthalmol.* 2021; 31(2):556-565.
15. Savastano MC, Dansingani KK, Rispoli M, et al. Classification of Haller vessel arrangements in acute and chronic central serous chorioretinopathy imaged with en face optical coherence tomography. *Retina* 2018; 38(6):1211-1215.
16. Pujari A, Surve A, Azad SV, et al. Optical coherence tomography angiography in central serous chorioretinopathy: the current clinical role and future perspectives. *Surv Ophthalmol.* Epub ahead of print 2021 May 14. doi: 10.1016/j.survophthal.2021.05.003.
17. Ng DS, Ho M, Chen LJ, et al. Optical coherence tomography angiography compared with multimodal imaging for diagnosing neovascular central serous chorioretinopathy. *Am J Ophthalmol.* Epub ahead of print 2021 Jun 8. doi: 10.1016/j.ajo.2021.05.029.

Patterns of Choroidal Venous Insufficiency Influencing Pachychoroid Disease

K Bailey Freund MD, Tommaso Bacci MD, Daniel J Oh MD, Michael Singer MD, and SriniVas Sadda MD

"Pachychoroid disease" is a relatively novel category of retinal disorder introduced in 2013 to define a forme fruste of central serous chorioretinopathy (CSC) characterized by retinal pigment epithelial (RPE) abnormalities presenting in eyes lacking a history or imaging evidence of subretinal fluid. This entity was named "pachychoroid pigment epitheliopathy" and was suggested to be part of a broader disease spectrum including central serous chorioretinopathy and other clinical presentations sharing imaging characteristics and alleged pathophysiology. Subsequent observations contributed to further define this complex of phenotypes.

The term "pachychoroid" contains an etymological reference to the supernormal choroidal thickness that has been reported in eyes with CSC using enhanced depth imaging OCT and that appears to be a common feature of conditions within the pachychoroid disease spectrum. However, the diagnosis of pachychoroid disease cannot rely on a specific choroidal thickness value since this parameter shows a great intra- and interindividual variability and is influenced by multiple physiologic and pathologic determinants. Nevertheless, choroidal thickness measurements incongruous with values typical of a patient's age, axial length, and ocular anatomy may be used diagnostically, especially in association with other characteristic multimodal imaging findings, including the following:

- Dilated choroidal veins, "pachyvessels," draining to dilated vortex ampullas
- Indocyanine green angiography (ICG-A) findings of delayed choroidal filling and choroidal vascular hyperpermeability around pachyvessels
- Inner choroidal flow attenuation leading to RPE changes, pachydrusen, and macular neovascularization
- Intervortex venous anastomoses

A relative choroidal thickening due to enlargement of deep choroidal veins may ultimately be implicated in mechanisms of inner choroidal and RPE damage and is interpreted as a sign of choroidal venous congestion. CSC pathophysiology as it relates to choroidal venous dysfunction dates back several decades, to when ICG-A was first introduced as a diagnostic tool to visualize the choroidal circulation. Shimizu, Kishi, and their collaborators described various patterns in eyes with pachychoroid disease, including persistent choroidal vascular abnormalities, vascular remodeling with formation of intervortex venous anastomoses, and asymmetric choroidal venous drainage of the macular region. The authors proposed that these alterations were consequences of the occurrence of impaired choroidal venous outflow, similar to changes in eyes with mechanical obstruction of vortex vein systems. Using ultrawide-field ICG-A, Pang and coworkers described dilated choroidal vessels and engorged vortex vein ampullas in CSC eyes, supporting outflow congestion as a possible factor contributing to the pathogenesis of this and other pachychoroid diseases. The idea that pachychoroid disease is related to alteration of the choroidal venous homeostasis has gained consensus in the scientific community. Nevertheless, mechanisms by which outflow congestion is produced in the choroid of eyes with pachychoroid disease remain poorly understood.

The aim of the present study was to compare patterns of choroidal venous drainage in eyes with pachychoroid disease to those of healthy subjects. By means of ultrawide-field ICG-A and swept-source OCT, we evaluated the contribution of each vortex vein system to the overall postequatorial choroidal venous outflow and how the distribution of choroidal venous drainage by quadrants may affect the topography of biomarkers of pachychoroid disease, namely choroidal vascular hyperpermeability, intervortex venous anastomoses, and choroidal thickness.

Selected Readings

1. Prünte C, Flammer J. Choroidal capillary and venous congestion in central serous chorioretinopathy. *Am J Ophthalmol*. 1996; 121(1):26-34.
2. Takahashi K, Kishi S. Remodeling of choroidal venous drainage after vortex vein occlusion following scleral buckling for retinal detachment. *Am J Ophthalmol*. 2000; 129(2):191-198.
3. Warrow DJ, Hoang QV, Freund KB. Pachychoroid pigment epitheliopathy. *Retina* 2013; 33(8):1659-1672.
4. Pang CE, Shah VP, Sarraf D, Freund KB. Ultra-widefield imaging with autofluorescence and indocyanine green angiography in central serous chorioretinopathy. *Am J Ophthalmol*. 2014; 158(2):362-371.
5. Cheung CMG, Lee WK, Koizumi H, Dansingani K, Lai TYY, Freund KB. Pachychoroid disease. *Eye* 2019; 33(1):14-33.
6. Sakurada Y, Fragiotta S, Leong BCS, Parikh R, Hussnain SA, Freund KB. Relationship between choroidal vascular hyperpermeability, choriocapillaris flow density, and choroidal thickness in eyes with pachychoroid pigment epitheliopathy. *Retina* 2020; 40(4):657-662.
7. Matsumoto H, Kishi S, Mukai R, Akiyama H. Remodeling of macular vortex veins in pachychoroid neovasculopathy. *Sci Rep*. 2019; 9(1).
8. Spaide RF, Gemmy Cheung CM, Matsumoto H, et al. Venous overload choroidopathy: a hypothetical framework for central serous chorioretinopathy and allied disorders. *Prog Retin Eye Res*. Epub ahead of print 2021 May 21. doi: 10.1016/j.preteyeres.2021.100973.

Beyond Pachychoroid: Venous Overload Chorioretinopathy

Richard F Spaide MD

Attempts have been made to group diseases seemingly sharing similarities, but these groupings were based on epiphenomena, and not pathophysiologic mechanisms. For example, "pachychoroid" initially was based on the idea of some diseases causing a thickening choroid but this failed to include dozens of conditions that caused choroidal thickening. However, some diseases, such as central serous chorioretinopathy (CSC), do appear to share pathophysiologic mechanisms of disease with an array of disorders. Understanding the underlying abnormalities of CSC can help in understanding the related disorders.

In CSC, the macula is detached because of fluid leakage at the level of the retinal pigment epithelium. The fluid appears to originate from choroidal vascular hyperpermeability. The choroidal vascular findings, as elucidated by recent OCT and wide-field indocyanine green (ICG) angiographic evaluation, show that eyes with CSC have many of the same venous patterns found in eyes following occlusion of the vortex veins or carotid cavernous sinus fistulas (CCSF). The eyes show delayed choroidal filling, dilated veins, intervortex venous anastomoses, and choroidal vascular hyperpermeability. While patients with occlusion of the vortex veins or CCSF have extraocular abnormalities accounting for the venous outflow problems, eyes with CSC appear to have venous outflow abnormalities as an intrinsic phenomenon. Control of venous outflow from the eye involves a Starling resistor effect, in which there appears to be an abnormal restriction to venous outflow. Similar choroidal vascular abnormalities have been found in peripapillary pachychoroid syndrome. Peripapillary pachychoroid syndrome has intervortex venous anastomoses located in the peripapillary region, while in CSC these are in the macular region. Choroidal hemangiomas exhibit a hyperdynamic blood flow within the lesion that seem to overload the venous system of the choroid. These eyes show intervortex venous anastomoses and areas of hyperpermeability, like those seen in CSC, in areas away from the hemangioma.

These diseases vary according to their underlying etiologies but are linked by the venous overloading in the choroid, increased choriocapillaris pressure, with leakage and capillary loss, all of which can lead to significant vision loss. The venous changes in the choroid mimic the pathophysiologic changes seen in chronic venous insufficiency elsewhere in the body. To a greater extent than previous proposals, choroidal venous overload provides a unifying concept and theory for an improved understanding of the pathophysiology and classification of this group of diseases.

How Does the Venous Outflow Pathway Change in Central Serous Chorioretinopathy?

Shoji Kishi MD PhD, Hidetaka Matsumoto MD, and Hideo Akiyama MD

Background

It has been recognized that the basic lesion of central serous chorioretinopathy (CSC) is chronic choroidal venous stasis, which is the starting point of pachychoroid spectrum diseases.[1] Ultrawide-field indocyanine green (ICG) angiography revealed congestion of 1 or more vortex vein ampullas in CSC.[2] This finding suggests that the cause of CSC is stenosis in the scleral canal of the vortex vein. We will discuss how the choroidal drainage route is altered by chronic congestion of the vortex vein.

Dilatation of Asymmetric Vortex Vein

Hayreh described that venous drainage of the choroid was divided into 4 quadrants by horizontal and vertical watershed zones.[3] Each vortex vein independently serves each quadrant. We compared the symmetry of the superior and inferior vortex vein along the horizontal watershed in normal eyes and CSC.[4] In normal eyes, both vortex veins were symmetrically distributed in 62% but asymmetric in 38%. In CSC, that symmetry is generally lost. Unilateral or bilateral vortex veins were dilated. Watershed zone had frequently disappeared because of the anastomosis (Figure 1).

Geographic Filling Delay in the Region of Dilated Asymmetric Vortex Veins

Filling delay areas in the choriocapillaris and dilated vortex vein regions were well overlapped in acute CSC (Figure 2).[5] Increased choroidal thickness was attributed to dilated vortex veins. These findings suggest that the blood flow into the choriocapillaris is delayed as a result of congestion of the dominant vortex veins that supply this geographic area. In chronic CSC, the boundary between the superior and inferior vortex veins becomes indistinct due to the anastomosis between the two. The thickness of the choroid also becomes thinner. This is probably because anastomosis creates a compensatory outflow tract.

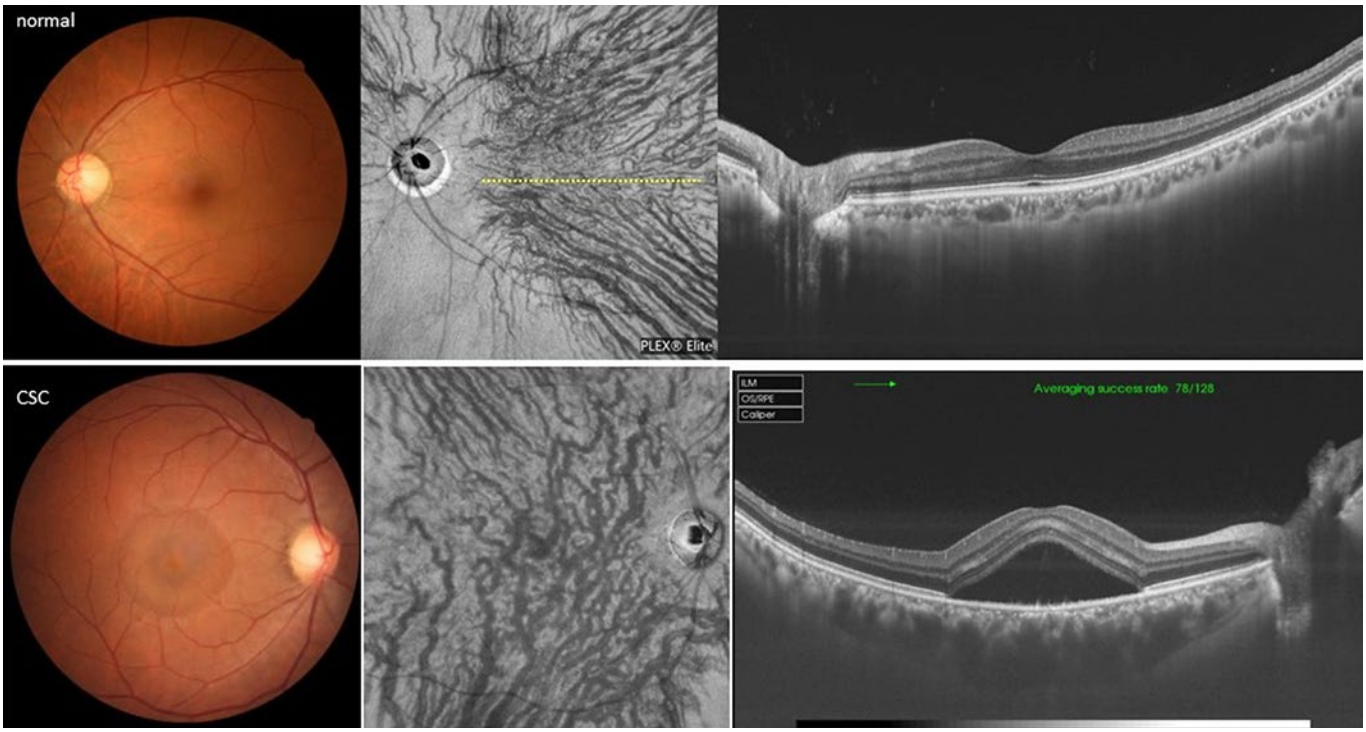


Figure 1. Upper: normal eye. En face imaging shows symmetry between the upper and lower vortex veins across the horizontal watershed (yellow dashed line). B-scan image shows no pachychoroid. Lower: CSC. Serous retinal detachment in the macula. En face imaging shows asymmetric vortex veins, with a predominant distribution of inferior vortex veins and dilated vascular lumen. Watershed is not identified. B-scan image shows pachychoroid.

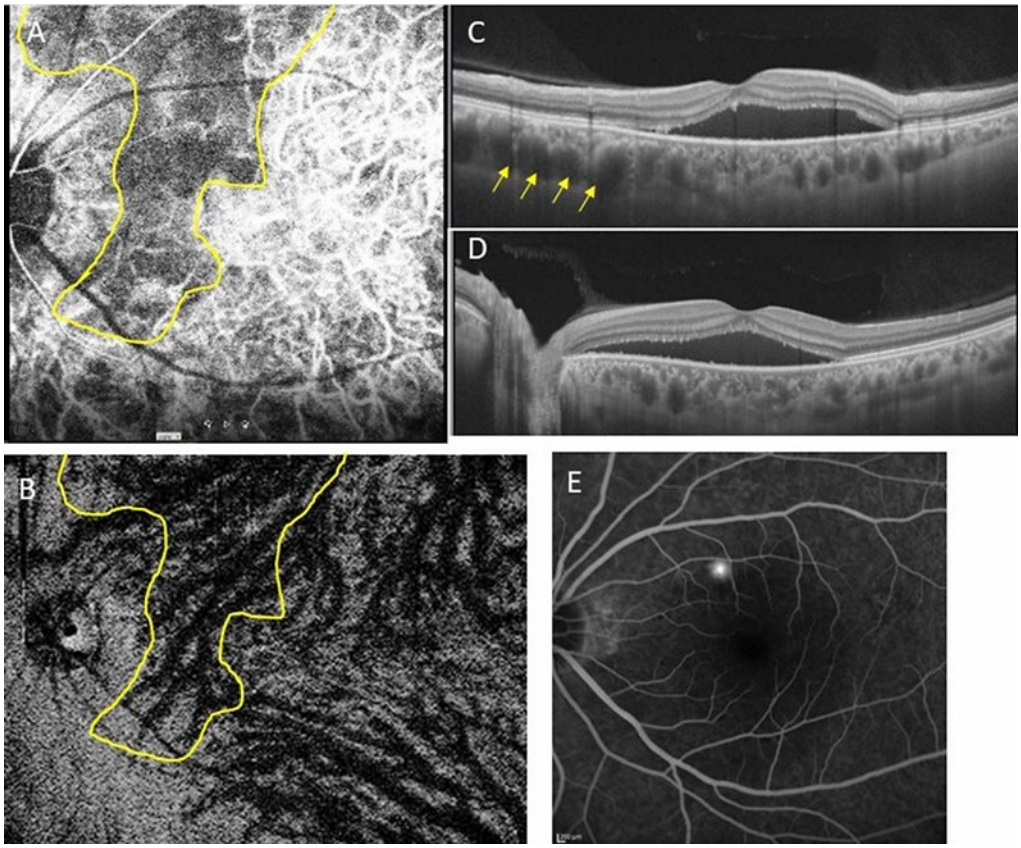


Figure 2. Acute CSC. Early phase ICG angiography shows geographic area of filling delay (A), which corresponds with the area of dilated asymmetric vortex vein in en face imaging (B). OCT B-scan images (C, D) show dilated superior vortex veins (yellow arrows). Fluorescein angiography shows dye leakage on the dilated vortex vein.

Anastomosis at Horizontal Watershed Zone

We evaluated en face imaging of 47 eyes with treatment naïve CSC. Anastomosis between superior and inferior vortex vein was seen in 85%. In these eyes, the horizontal watershed zone had disappeared. Anastomotic veins were dilated and hyperpermeable in ICG angiography (Figure 3). In the remaining 15%, macular vortex veins were dilated, but watershed was identified. Subfoveal thickness was significantly thicker in the eyes with anastomosis than in the eyes with no anastomosis because dilated anastomotic veins were located at the macular area.

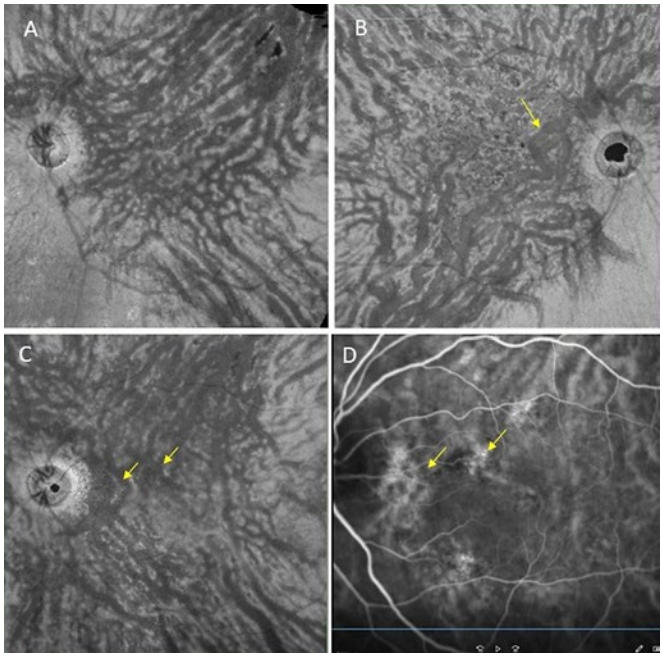


Figure 3. Patterns of anastomosis between superior and inferior vortex veins. (A) Superior vortex is predominant. Numerous anastomosis at watershed. (B) Inferior vortex vein is predominant with marked dilatation. Dilated anastomotic vein is seen (yellow arrow). (C) Anastomosis at peripapillary (yellow arrows). Superior vortex veins are dilated. (D) ICG angiography of C shows hyperpermeability in dilated anastomotic vein (yellow arrows).

CNV Arises From the Anastomosis in Pachychoroid Neovasculopathy

OCT angiography has made it possible to detect CNV within PEDs. As a result, many lesions that were previously thought to be chronic CSC can now be diagnosed as pachychoroid neovasculopathy (PNV). In PNV, venous anastomosis is more evident at the watershed. CNV arises from the anastomosis.[6] Anastomotic vessel shows dilatation and hyperpermeability (Figure 4).

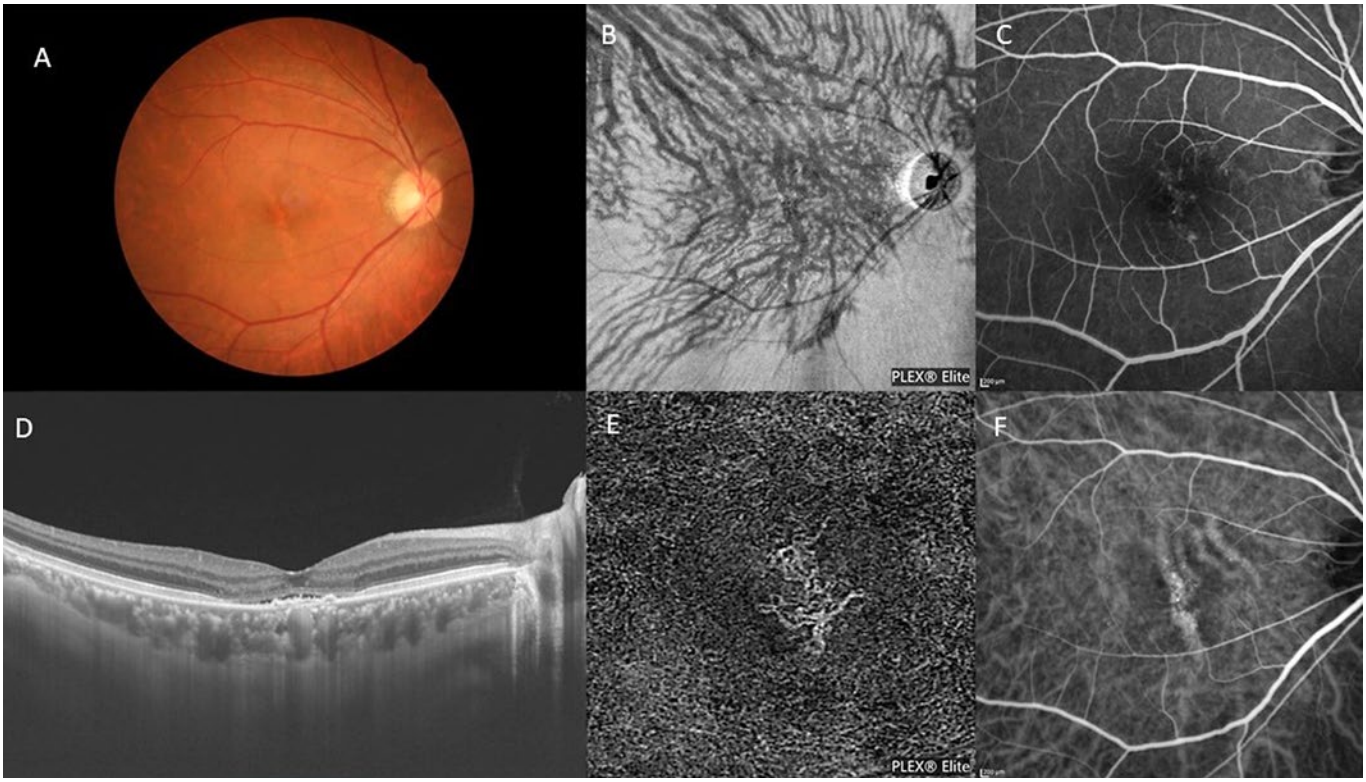


Figure 4. (A) Pachychoroid neovasculopathy. (B) En face image shows marked venous anastomosis at watershed. (C) Fluorescein angiography shows faint hyperfluorescence. (D) B-scan image shows slight serous retinal detachment with flat pigment epithelial detachment (PED). (E) OCT angiography revealed CNV beneath the PED, which arises from the anastomosis. (F) ICG angiography shows that anastomotic vessels are dilated and hyperpermeable.

Remodeling of Choroidal Drainage Route in Vortex Vein Occlusion

We previously reported how choroidal veins respond to the vortex vein occlusion by scleral buckling.[7] In case of 1 temporal vortex vein occlusion, venous anastomosis developed across the horizontal watershed. In eyes with more than 2 vortex veins occluded by scleral encircling, a new drainage route was developed through the intervortex anastomosis across the horizontal and vertical watersheds (Figure 5). The choroidal veins have a great deal of plasticity that enables remodeling of the drainage routes, depending on the pressure gradient.

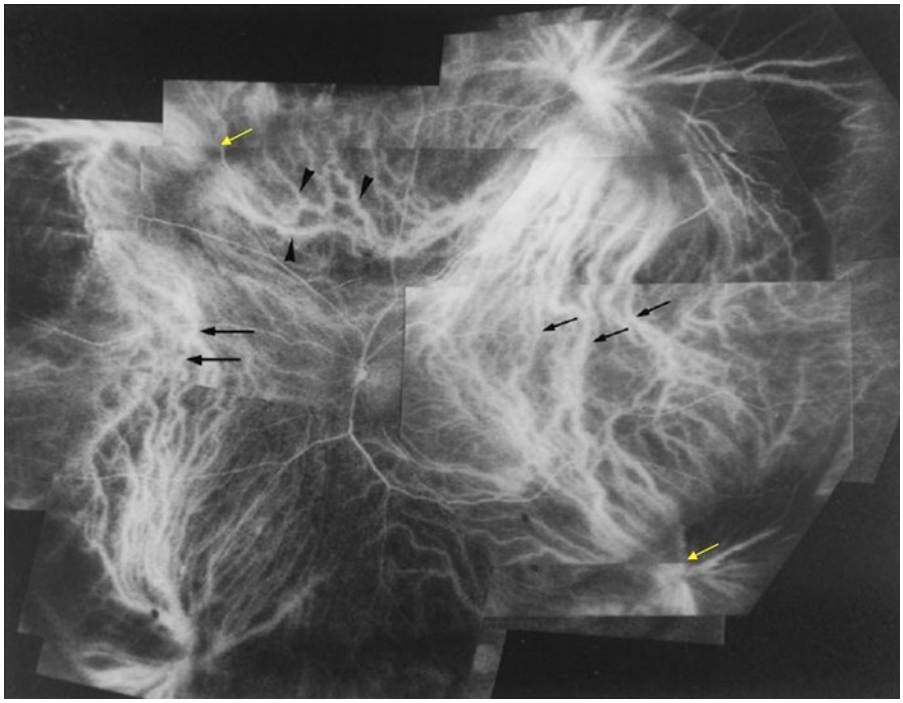


Figure 5. Intervortex venous anastomosis. Scleral encircling was performed 4 months before the ICG angiography. Superonasal and inferotemporal ampullas were attenuated (yellow arrows). New drainage routes were developed through the anastomosis across the horizontal (arrows) and vertical watersheds (arrowheads).

Conclusions

Remodeling of venous drainage route frequently develops though the anastomosis across the watersheds in CSC and other pachychoroid diseases.[8] Long-standing vortex vein congestion may lead to the development of pachychoroid spectrum diseases. Choroidal congestion may be compensated for by new drainage routes formed via intervortex venous anastomosis.

References

1. Dansingani KK, Balaratnasingam C, Naysan J, Freund KB. En face imaging of pachychoroid spectrum disorders with swept-source optical coherence tomography. *Retina* 2016; 36(3):499-516.
2. Pang CE, Shah VP, Sarraf D, Freund KB. Ultra-widefield imaging with autofluorescence and indocyanine green angiography in central serous chorioretinopathy. *Am J Ophthalmol*. 2014; 158(2):362-371.
3. Hayreh SS. Segmental nature of the choroidal vasculature. *Br J Ophthalmol*. 1975; 59:631e648.
4. Hiroe T, Kishi S. Dilatation of asymmetric vortex vein in central serous chorioretinopathy. *Ophthalmol Retina*. 2018; 2(2):152-161.
5. Kishi S, Matsumoto H, Sonoda S, Hiroe T, Sakamoto T, Akiyama H. Geographic filling delay of the choriocapillaris in the region of dilated asymmetric vortex veins in central serous chorioretinopathy. *PLoS One*. 2018; 13(11):e0206646.
6. Matsumoto H, Kishi S, Mukai R, Akiyama H. Remodeling of macular vortex veins in pachychoroid neovasculopathy. *Sci Rep*. 2019; 9(1):14689.
7. Takahashi K, Kishi S. Remodeling of choroidal venous drainage after vortex vein occlusion following scleral buckling for retinal detachment. *Am J Ophthalmol*. 2000; 129:191-198.
8. Matsumoto H, Hoshino J, Mukai R, et al. Vortex vein anastomosis at the watershed in pachychoroid spectrum diseases. *Ophthalmol Retina*. 2020; 4(9):938-945.

What's New in Retinal Dystrophies?

Jacque L Duncan MD

Retinal dystrophies and degenerations are among the most challenging diseases that ophthalmologists encounter. They are exceptionally heterogeneous: each broad diagnostic category like retinitis pigmentosa results from disease-causing variations in at least 60 distinct genes and likely represents at least as many different diseases. Furthermore, each gene is capable of causing distinct manifestations: for example, pathogenic variants in *RDS* and *ABCA4* have been associated with disease ranging from maculopathy to cone-rod dystrophy to widespread rod-cone degeneration. Many of the diagnostic tools used to characterize retinal degenerations, including genetic testing, psychophysical testing, and electrophysiological testing, are not used commonly by many retinal specialists, making it challenging to accurately characterize and diagnose patients. The range of disease causes and manifestations can be overwhelming. In addition, treatments for retinal degenerations have traditionally ranged from limited to nonexistent.

However, it has never been more important for retinal specialists to understand how to diagnose, characterize, and manage patients with inherited retinal degenerations. To date, genetic research has identified over 300 genes associated with inherited retinal degenerations,[1] and the number increases each year. Genetic testing using next-generation sequencing panels can identify the genetic cause of retinal degeneration in up to 70% of patients with inherited retinal degenerations.[2] For most patients with inherited retinal degenerations living in the United States and in certain countries outside the U.S., genetic testing and genetic counseling are available through sponsored programs with support from nonprofit and for-profit entities. Increased genetic testing has expanded the number of pathogenic and likely pathogenic variants in previously reported genes, and has provided data for the discovery of new genes associated with retinal degenerations.

The role of genetic testing became critical in December 2017, when the U.S. Food and Drug Administration approved voretigene neparvovec for patients with retinal degeneration with biallelic pathogenic variants in *RPE65*.[3] This represented the first gene-specific therapy approved for treatment of human disease and stimulated many investigators and sponsors to develop gene therapies for other diseases, including achromatopsia, choroideremia, X-linked retinoschisis, X-linked retinitis pigmentosa, and even AMD. Since the adeno-associated viral (AAV) vector that was successfully used to deliver *RPE65* can accommodate genes up to about 4 kb in size, alternative approaches using lentivirus were developed for large genes, including *MYO7A*-related Usher syndrome type 1 and *ABCA4*-related Stargardt disease. Approaches including antisense oligonucleotide therapies were developed for large genes with common variants that introduce splicing defects in genes, including *CEP290* and *USH2A*, and intravitreal injection of antisense oligonucleotides for these 2 genes have been shown to be safe, with preliminary evidence of efficacy in Phase 2 studies.[4] Gene editing using clustered regularly interspaced short palindromic repeats (CRISPR) may offer a new approach for treatment of large genes that exceed the carrying capacity of AAV and potentially also for autosomal dominant retinal degenerations. The Nobel Prize in chemistry was awarded to inventors of CRISPR technology in 2020 in recognition of the potential this novel approach has to treat a wide range of diseases, and early reports of safety using CRISPR to treat photoreceptors in the eyes of patients affected with *CEP290*-related retinal degeneration were reported in May 2021.

Gene-specific therapies offer the potential to slow the course of vision loss by correcting the disease-causing mutation, and in some retinal degenerations like *RPE65*-related retinal degeneration, they are effective in improving vision of photoreceptors that have not degenerated. However, at least 30% of patients who undergo genetic testing do not have variants in genes known to cause retinal degeneration that are included in next-generation sequencing panels, and for these patients, treatments that intervene in pathways that cause retinal degeneration may be helpful. For example, treatments that prevent photoreceptor degeneration[5] or reduce oxidative stress may prolong photoreceptor survival and improve visual function.[6] Many patients have advanced disease where few to no photoreceptors remain to treat with gene-specific therapies. For these patients, therapies that may restore some vision include using stem cells to revitalize photoreceptors that have lost outer segments.[7] Prosthetic devices use electrical stimulation of inner retinal cells to elicit vision in patients with advanced vision loss caused by retinitis pigmentosa[8] and atrophic AMD.[9] Inner retinal cells that are not intrinsically sensitive to light can be treated with light-sensitive proteins to confer photosensitivity to cells when photoreceptors have been lost; this approach is called optogenetics. Clinical trials of optogenetics have recently demonstrated partial restoration of sight to patients with profound vision loss from retinitis pigmentosa,[10] and many other approaches are either in clinical trials or preclinical stages of development.[11]

In summary, retinal degenerations represent one of the most promising areas of unmet need in ophthalmology, with multiple trials of experimental therapies in development. Retinal specialists need to be informed about new developments and opportunities to care for their patients with these diseases.

References

1. Number of genes and loci by disease category. RetNet (Retinal Information Network) website. https://sph.uth.edu/retnet/sum-dis.htm#A-genes.
2. Consugar MB, Navarro-Gomez D, Place EM, et al. Panel-based genetic diagnostic testing for inherited eye diseases is highly accurate and reproducible, and more sensitive for variant detection, than exome sequencing. *Genet Med*. 2015; 17(4):253-261.
3. Russell S, Bennett J, Wellman JA, et al. Efficacy and safety of voretigene neparvovec (AAV2-hRPE65v2) in patients with RPE65-mediated inherited retinal dystrophy: a randomised, controlled, open-label, Phase 3 trial. *Lancet* 2017; 390(10097):849-860.
4. Cideciyan AV, Jacobson SG, Drack AV, et al. Effect of an intravitreal antisense oligonucleotide on vision in Leber congenital amaurosis due to a photoreceptor cilium defect. *Nat Med*. 2019; 25(2):225-228.

5. Leveillard T, Fridlich R, Clerin E, et al. Therapeutic strategy for handling inherited retinal degenerations in a gene-independent manner using rod-derived cone viability factors. *C R Biol*. 2014; 337(3):207-213.

6. Campochiaro PA, Iftikhar M, Hafiz G, et al. Oral N-acetylcysteine improves cone function in retinitis pigmentosa patients in Phase I trial. *J Clin Invest*. 2020; 130(3):1527-1541.

7. Stern JH, Tian Y, Funderburgh J, et al. Regenerating eye tissues to preserve and restore vision. *Cell Stem Cell*. 2018; 23(3):453.

8. Delyfer MN, Gaucher D, Mohand-Said S, et al. Improved performance and safety from Argus II retinal prosthesis post-approval study in France. *Acta Ophthalmol*. Epub ahead of print 2020 Dec 23. doi: 10.1111/aos.14728.

9. Palanker D, Le Mer Y, Mohand-Said S, et al. Photovoltaic restoration of central vision in atrophic age-related macular degeneration. *Ophthalmology* 2020; 127(8):1097-1104.

10. Sahel JA, Boulanger-Scemama E, Pagot C, et al. Partial recovery of visual function in a blind patient after optogenetic therapy. *Nat Med*. Epub ahead of print 2021 May 24. doi: 10.1038/s41591-021-01351-4.

11. Berry MH, Holt A, Salari A, et al. Restoration of high-sensitivity and adapting vision with a cone opsin. *Nat Commun*. 2019; 10(1):1221.

Blood–Brain Barrier Disruption Maculopathy

Phoebe Lin MD PhD

Introduction

Osmotic blood–brain barrier disruption (BBBD) is a method to enhance penetration of chemotherapy used to treat CNS tumors. The procedure involves intra-arterial injection of warmed hypertonic mannitol to disrupt tight junctions of vascular endothelial cells. In this study, we characterized a pigmentary maculopathy that occurs in CNS tumor patients who have undergone BBBD therapy.

Results

Of 283 patients who were treated with BBBD, 68 had documented ophthalmic examination and/or retinal imaging after their BBBD start date, and 65 patients had sufficient ocular media clarity to be included in the study. A pigmentary maculopathy was present in 49% of patients (32/65), with 4 main patterns identified (see Figure 1): (1) central retinal pigment epithelial stippling, (2) reticular pigmentary changes, (3) parafoveal bull's eye, and (4) parafoveal or subfoveal geographic atrophy. We found that the number of BBBD sessions, but not other factors such as CNS tumor type, was associated with maculopathy development (OR 1.3, $P = .001$).

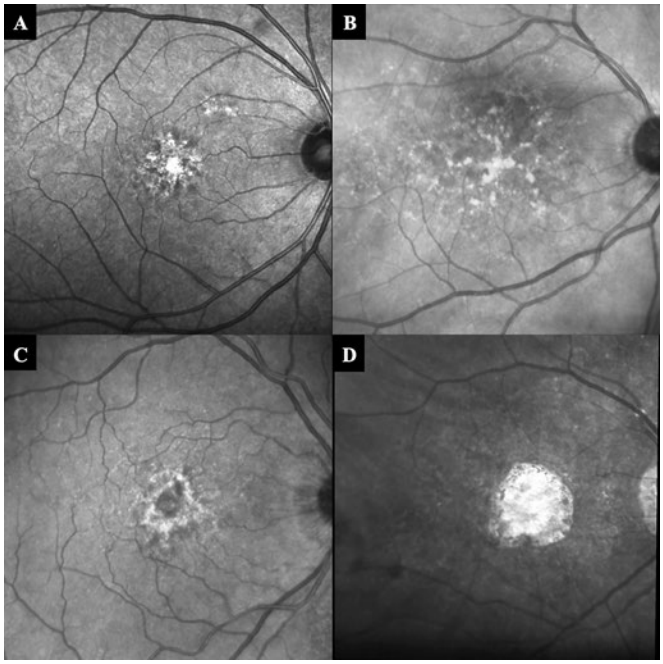


Figure 1

Conclusions

BBBD maculopathy occurs as a dose-dependent effect of treatment sessions. We recommend education of CNS tumor patients who are about to undergo BBBD as well as ophthalmic monitoring.

The Role of the Intestinal Microbiome in Retinal Diseases

Sebastian Wolf MD PhD, Denise Zysset-Burri PhD, and Martin Zinkernagel MD PhD

The microbes within the human gastrointestinal tract are referred to as the "intestinal gut microbiome." Playing a major role in the digestion of food and influencing 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. The gut microbiome is a complex ecosystem of more than 100 trillion microbes that influence human physiology, metabolism, nutrition, and immune function.

The intestinal microbiome plays a central role in human health and disease. While its composition is relatively stable throughout adulthood, the microbial balance starts to deteriorate in later life stages. Thus, in order to maintain a good quality of life, including the prevention of age-associated diseases in the elderly, it is important to understand the dynamics of the intestinal microbiome. 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 that AMD patients have 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. Additionally, we have found an association between the intestinal microbiome and the complement system in neovascular AMD.

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.

Suggested Readings

1. Zinkernagel MS, Zysset-Burri DC, Keller I, et al. Association of the intestinal microbiome with the development of neovascular age-related macular degeneration. *Sci Rep*. 2017; 7:40826.
2. Zysset-Burri DC, Keller I, Berger LE, et al. Associations of the intestinal microbiome with the complement system in neovascular age-related macular degeneration. *NPJ Genom Med*. 2020; 5:34.
3. Rowan S, Jiang S, Korem T, et al. Involvement of a gut-retina axis in protection against dietary glycemia-induced age-related macular degeneration. *Proc Natl Acad Sci U S A*. 2017; 114(22):E4472-E4481.
4. Zysset-Burri DC, Keller I, Berger LE, et al. Retinal artery occlusion is associated with compositional and functional shifts in the gut microbiome and altered trimethylamine-N-oxide levels. *Sci Rep*. 2019; 25:15303.
5. Fu J, Bonder MJ, Cenit MC, et al. The gut microbiome contributes to a substantial proportion of the variation in blood lipids. *Circ Res*. 2015; 117:817-824.
6. Karlsson FH, Fak F, Nookaew I, et al. Symptomatic atherosclerosis is associated with an altered gut metagenome. *Nat Commun*. 2012; 3:1245.
7. Tang WH, Hazen SL. The contributory role of gut microbiota in cardiovascular disease. *J Clin Invest*. 2014; 124:4204-4211.
8. Turnbaugh PJ, Hamady M, Yatsunenko T, et al. A core gut microbiome in obese and lean twins. *Nature* 2009; 457:480-484.
9. Thevaranjan N, Puchta A, Schulz C, et al. Age-associated microbial dysbiosis promotes intestinal permeability, systemic inflammation, and macrophage dysfunction. *Cell Host Microbe*. 2017; 21:455-466 e454.
10. Segata N, Izard J, Waldron L, et al. Metagenomic biomarker discovery and explanation. *Genome Biol*. 2011; 12:R60.
11. Human Microbiome Project C. A framework for human microbiome research. *Nature* 2012; 486:215-221.
12. Koren O, Spor A, Felin J, et al. Human oral, gut, and plaque microbiota in patients with atherosclerosis. *Proc Natl Acad Sci U S A*. 2011; 108 suppl 1:4592-4598.
13. Faith JJ, Guruge JL, Charbonneau M, et al. The long-term stability of the human gut microbiota. *Science* 2013; 341:1237439.
14. Ley RE, Turnbaugh PJ, Klein S, Gordon JI. Microbial ecology: human gut microbes associated with obesity. *Nature* 2006; 444:1022-1023.

Update on Uveitic Macular Edema

Douglas A Jabs MD MBA

Annotated Bibliography

1. Tomkins-Netzer O, Lightman S, Drye L, Kempen JH, Holland GN, Rao NA, Stawell RJ, Vitale A, Jabs DA for the Multicenter Uveitis Steroid Treatment (MUST) Trial Research Group. Outcome of treatment of uveitic macular edema: the Multicenter Uveitis Steroid Treatment (MUST) trial 2-year results. *Ophthalmology* 2015; 122:2351-2359. *Uveitic macular edema improves in 71% of eyes and resolves in 60% by 2 years of therapy. Even with control of the inflammation by systemic therapy, 62% of eyes with uveitic macular needed 1-2 adjunctive regional corticosteroid injections in the first 2 years.*
2. Tomkins-Netzer O, Lightman S, Burke AE, Sugar EA, Lim L, Jaffe G, Altaweel MM, Kempen JH, Holbrook JT, Jabs DA. Seven-year outcomes of uveitic macular edema: the Multicenter Uveitis Steroid Treatment (MUST) trial and follow-up study results. *Ophthalmology* 2020; 128:719-728. *Resolution of uveitic macular edema occurred in 94% of eyes by 7 years of follow-up. Among eyes with resolved macular edema, 43% experienced a recurrence of the macular edema by 7 years. Resolution of macular edema was associated with an improvement in visual acuity.*
3. Thorne JE, Sugar EA, Holbrook JT, Burke AE, Altaweel MM, Vitale AT, Acharya NR; Kempen JH, Jabs DA. Periocular triamcinolone versus intravitreal triamcinolone versus intravitreal dexamethasone implant for the treatment of uveitic macular edema: the PeriOcular versus INTravitreal corticosteroids for uveitic macular edema (POINT) trial. *Ophthalmology* 2019; 126:283-295. *Intravitreal corticosteroid injections, either of triamcinolone acetonide or the dexamethasone implant (Ozurdex), were superior to periocular corticosteroid injections of triamcinolone acetonide for the treatment of uveitic macular edema for improvement in and resolution of edema and improvement in visual acuity. There were no significant differences between the 2 intravitreal drugs. Elevation of IOP to ≥30 mmHg was infrequent (≤6%) and similar among the 3 groups.*
4. Lehpamer B, Moshier E, Pahk P, Goldberg N, Ackert J, Godbold J, Jabs DA. Epiretinal membranes in uveitic macular edema: effect on vision and response to therapy. *Am J Ophthalmol*. 2014; 157:1048-1055. *Epiretinal membranes that distort the retinal surface are associated with a failure of medical therapy to improve uveitic macular edema and failure to improve vision loss. These data suggest that severe epiretinal membranes with uveitic macular edema should be approached surgically.*
5. Kempen JH, Sugar EA, Jaffee GJ, Acharya NR, Dunn JP, Elner SG, Lightman SL, Thorne JE, Vitale AT, Altaweel MM; Multicenter Uveitis Steroid Treatment (MUST) Trial Research Group. Fluorescein angiography versus optical coherence tomography for diagnosis of uveitic macular edema. *Ophthalmology* 2013; 120:1852-1859. *Fluorescein angiography and OCT are discordant for the diagnosis of uveitic macular edema in ~25% of eyes, suggesting the need for both modalities.*

Update on Intraocular Sustained Drug Delivery for Uveitis

Glenn J Jaffe MD

Intraocular sustained drug delivery has increasingly become available to treat retinal and ocular inflammatory diseases. Sustained drug delivery systems include transscleral delivery techniques, intravitreal implants, intravitreal injection, suprachoroidal infusion, subretinal implants, refillable reservoirs, and gene therapy approaches. The U.S. FDA has approved specific intravitreal implants. Approved nonbiodegradable implants that release drug over 2.5-3 years include the surgically implanted fluocinolone acetonide implant, approved for uveitis affecting the posterior segment, and injectable fluocinolone acetonide implants, approved for chronic diabetic macular edema and uveitis. A biodegradable injectable dexamethasone implant that releases over 6 weeks to 3 months is approved to treat macular edema and uveitis.

Sustained drug delivery systems are also under development for uveitis. A suprachoroidal dexamethasone infusion system has been designed to treat uveitic macular edema. Drug is delivered to the suprachoroidal space through a specially designed needle injector. In the Phase 3 Peachtree trial, this implant resulted in improved visual acuity and decreased edema when compared to controls, among eyes with all types of uveitic macular edema. The rates of elevated IOP were similar to controls, and no eye developed endophthalmitis. Eyevensys has developed a novel gene therapy approach in which a genetically engineered plasmid that encodes for an antitumor necrosis factor alpha fusion protein is delivered to the ciliary body by an electrotransfection system. In essence, the ciliary body functions as a protein factory to produce biologically active therapeutic protein for at least 6 months. In a Phase 1 clinical trial, there were no serious adverse events, and 3/9 subjects had >10 letters of visual acuity gain. A Phase 2 trial is under way.

The future is very bright for intraocular sustained drug delivery for uveitis. In the near future, it is likely that new intraocular sustained delivery systems will be approved by regulatory agencies for the clinician to use to treat ocular inflammatory eye diseases.

Novel Therapies in Development for Noninfectious Intermediate, Posterior, and Pan-Uveitis

Quan Dong Nguyen MD

I. Introduction: Cytokine Network in Uveitis

II. Selected Novel Clinical Trials in Uveitis and Ocular Inflammatory Diseases

A. Interleukin-17 inhibition

Izokibep is a novel bispecific agent, potently targeting both subunits of IL-17A as well as albumin. Izokibep has been specifically designed to utilize the strengths of a novel technology platform to create a very small protein drug (18 kDa, an eighth of the size of an antibody) with very high apparent affinity to IL-17A and antibody-like half-life due to the strong binding affinity to serum albumin. The LINNAEA Study has been designed to evaluate the role of izokibep as a first-line therapeutic option for active noninfectious uveitis as well as a steroid-sparing immunomodulatory agent. The trial will evaluate the efficacy, safety, and tolerability of izokibep as compared to standard of care.

B. T-cell inhibition

T cells are known to play a fundamental role in inducing ocular inflammation, and PP-001 inhibits T-cell proliferation and suppresses cytokine expression by inhibition of dihydroorotate dehydrogenase (DHOODH). DHOODH inhibition leads to reduction in levels of cellular pyrimidine, which leads to reduction of T-cell proliferation. In addition, DHOODH inhibition also leads to downregulation of IL-17, interferon-gamma, and VEGF.

III. Summary: The Future of Uveitis Therapy

Selected References

1. Agarwal A, Hassan M, Sepah YJ, Do DV, Nguyen QD. Subcutaneous repository corticotropin gel for non-infectious panuveitis: reappraisal of an old pharmacologic agent. *Am J Ophthalmol Case Rep*. 2016; 4:78-82.
2. Dick AD, Tugal-Tutkun I, Foster S, et al. Secukinumab in the treatment of noninfectious uveitis: results of three randomized, controlled clinical trials. *Ophthalmology* 2013; 120(4):777-787.
3. Esterbauer H, Schaur RJ, Zollner H. Chemistry and biochemistry of 4-hydroxynonenal, malonaldehyde and related aldehydes. *Free Radic Biol Med*. 1991; 11(1):81-128.
4. Hamzaoui K, Hamzaoui A, Guemira F, Bessioud M, Hamza M, Ayed K. Cytokine profile in Behçet's disease patients: relationship with disease activity. *Scand J Rheumatol*. 2002; 31(4):205-210.
5. Hassan M, Karkhur S, Bae JH, et al. New therapies in development for the management of non-infectious uveitis: a review. *Clin Experiment Ophthalmol*. 2019; 47(3):396-417.
6. Heissigerova J, Callanan D, de Smet MD, et al. Efficacy and safety of sarilumab for the treatment of posterior segment noninfectious uveitis (SARIL-NIU): the Phase 2 SATURN study. *Ophthalmology* 2019; 126(3):428-437.
7. Huang JF, Zhang Y, Hirakawa B. Evaluation of JAK inhibition with topical tofacitinib in experimental autoimmune uveitis model (EAU) [Abstract]. Association for Research in Vision and Ophthalmology (ARVO); May 5-9, 2013; Seattle, WA.
8. Hueber W, Patel DD, Dryja T, et al. for the Psoriasis Study Group; Durez P, Tak PP, Gomez-Reino JJ for the Rheumatoid Arthritis Study Group; Foster SC, Kim RY, Samson MC, et al. for the Uveitis Study Group; Rose K, Haider A, Di Padova F. Effects of AIN457, a fully human antibody to interleukin-17A, on psoriasis, rheumatoid arthritis, and uveitis. *Sci Transl Med*. 2010; 52(2):52ra72
9. Kavanaugh A, Kremer J, Ponce L, et al. Filgotinib (GLPG0634/GS-6034), an oral selective JAK1 inhibitor, is effective as monotherapy in patients with active rheumatoid arthritis: results from a randomised, dose-finding study (DARWIN 2). *Ann Rheum Dis*. 2017; 76(6):1009-1019.
10. Letko E, Yeh S, Foster SC, Pleyer U, Brigell M, Grosskreutz CL; AIN457A2208 Study Group. Efficacy and safety of intravenous secukinumab in noninfectious uveitis requiring steroid-sparing immunosuppressive therapy. *Ophthalmology* 2015; 122(5):939-948.
11. Nguyen QD, Merrill PT, Clark WL, et al; Sirolimus study Assessing double-masKed Uveitis tReAtment (SAKURA) Study Group. Intravitreal sirolimus for noninfectious uveitis: a Phase III Sirolimus study Assessing double-masKed Uveitis tReAtment (SAKURA). *Ophthalmology* 2016; 123(11):2413-2423.
12. Nguyen QD, Merrill PT, Sepah YJ, et al. Intravitreal sirolimus for the treatment of noninfectious uveitis: evolution through preclinical and clinical studies. *Ophthalmology* 2018; 125(12):1984-1993.
13. O'Brien PJ, Siraki AG, Shangari N. Aldehyde sources, metabolism, molecular toxicity mechanisms, and possible effects on human health. *Crit Rev Toxicol*. 2005; 35(7):609-662.
14. Sepah YJ, Sadiq MA, Chu DS, et al. Primary (month-6) outcomes of the STOP-Uveitis Study: evaluating the safety, tolerability, and efficacy of tocilizumab in patients with non-infectious uveitis. *Am J Ophthalmol*. 2017; 183:71-80.

Uveitis Panel Discussion

Panel Moderator: Sunil K Srivastava MD

Panelists: Nisha Acharya MD, Stephen J Kim MD, Phoebe Lin MD PhD

NOTES

Telemedicine Screening for Diabetic Retinopathy Is Ready to Go

Jennifer I Lim MD

I. Telemedicine for Diabetic Retinopathy (DR)

A. Rationale: Growing DR screening burden globally: 415 million in 2015 to 642 million by 2040[1]

1. Telemedicine addresses access to care issues: travel, limited resources, time, specialist, rural areas.[2-3]

2. Screening at primary care visit is cost-effective, obviates need for referral and follow-up issues.

B. Specifications

1. Image capture

a. Office: fundus camera

b. Mobile: handheld camera or smartphone

2. Image interpretation: Human vs. artificial intelligence (AI)

3. Image storage and integration into EHR needed

C. Feasibility

1. Digital photography comparable to film color fundus photos

2. Technology supports remote screening: digital image transfer via internet or cloud-based software.

3. AI-based systems are comparable with reading center interpretation of images.

II. Effectiveness of Telemedicine for DR Screening

A. Increased rates of DR screening with high patient acceptance[4]

B. Good sensitivity for diabetic macular edema, early DR, more than mild DR, and vision-threatening DR

C. Cost-effective

D. Specialist follow-up for referral of advanced DR largely unknown: 9.5% saw specialist in 1 study[5]

III. Examples of DR Screening Systems Using Human Interpretation of Color Fundus Images

A. Appalachia Diabetic Retinopathy Network Telemedicine DR Screening: federally designated safety net clinic (FDSC)-based TDRS network of 22 sites[6]

1. 13,923 patient telescreening visits

a. 10,540 adequate photo quality

b. 2319 (22.0%) had DR.

c. 1604 (15.2%) required specialist referral.

2. Mean screening rate increased from 29.9% (baseline) to 47.7% by Year 1.

B. Rural and urban clinic studies show DR screening to be cost-effective worldwide.[7-8]

IV. AI-based Interpretation of DR Images for DR Screening

A. High sensitivity, specificity, and accuracy compared to reading center gradings[9-13]

B. IDx/DR: 87.2% sensitivity, 90.7% specificity, and 96% imageability for more than mild DR (mtmDR)[12]

C. EyeArt

1. 95.5% sensitivity and 87.8% specificity for mtmDR

2. 97% sensitivity, 90% specificity for vision-threatening DR (vtDR)

3. 88% did not require dilation.[13-14]

D. Other systems: handheld cameras/phones

References

1. Ogustova K, da Rocha FJ, Huang Y, et al. IDF Diabetes Atlas: global estimates for the prevalence of diabetes for 2015 and 2040. *Diabetes Res Clin Pract*. 2017; 128:40.

2. Andonegui J, Serrano L, Eguzkiza A. Diabetic retinopathy screening using tele-ophthalmology in a primary care setting. *J Telemed Telecare*. 2010; 16:429-432.

3. Raparia E, Husain D. COVID-19 launches retinal telemedicine into the next frontier. *Semin Ophthalmol*. 2021; 36(4):258-263.

4. Agrawal S, Strzelec B, Poręba R, Agrawal A, Mazur G. Clinical characteristics, preventive care and attitude to telemedicine among patients with diabetic retinopathy: a cross-sectional study. *J Clin Med*. 2021; 10(2):249.

5. Benjamin JE, Sun J, Cohen D, et al. A 15-month experience with a primary care-based telemedicine screening program for diabetic retinopathy. *BMC Ophthalmol*. 2021; 21(1):70.

6. de Carvalho AB, Ware SL, Lei F, Bush HM, Sprang R, Higgins EB. Implementation and sustainment of a statewide telemedicine diabetic retinopathy screening network for federally designated safety-net clinics. *PLoS One* 2020; 15(11):e0241767.

7. Gao X, Park CH, Dedrick K, et al. Use of telehealth screening to detect diabetic retinopathy and other ocular findings in primary care settings. *Telemed J E Health*. 2019; 25:802-807.

8. Chin EK, Ventura BV, See K-Y, Seibles J, Park SS. Nonmydriatic fundus photography for teleophthalmology diabetic retinopathy screening in rural and urban clinics. *Telemed J E Health*. 2014; 20(2):102-108.

9. Gulshan V, Peng L, Coram M, et al. Development and validation of a deep learning algorithm for detection of diabetic retinopathy in retinal fundus photographs. *JAMA* 2016; 316(22):2402-2410.

10. Ting DSW, Cheung CY, Lim G, et al. Development and validation of a deep learning system for diabetic retinopathy and related eye diseases using retinal images from multiethnic populations with diabetes. *JAMA* 2017; 318(22):2211-2223.

11. Mokhashi N, Grachevskaya, Cheng L, et al. A comparison of artificial intelligence and human diabetic retinal image interpretation in an urban health system. *J Diabetes Sci Technol*. Epub ahead of print 2021 Mar 10. doi: 10.1177/1932296821999370.

12. Abramoff MD, Lavin PT, Birch M, Shah N, Folk JC. Pivotal trial of an autonomous AI-based diagnostic system for detection of diabetic retinopathy in primary care offices. *NPJ Digit Med*. 2018; 39:1-8.

13. Ipp E, Liljenquist D, Bode B, et al; for the EyeArt Study Group. Efficacy and safety of the EyeArt artificial intelligence system for detecting diabetic retinopathy: results from a pivotal clinical study. In press.

14. Lim JI, Bhaskaranand M, Ramachandra C, Regillo CD, Sadda SR. Artificial intelligence detection of diabetic retinopathy: subgroup comparison of the EyeArt system with ophthalmologists' dilated exams. In press.

Telemedicine Screening for Diabetic Retinopathy Has a Ways to Go

Christina Y Weng MD MBA

Position Statement

Vision loss from diabetic retinopathy (DR) is largely preventable with timely detection and treatment, but only 50%-65% of patients with diabetes are compliant with ophthalmic screening recommendations,[1] and that rate is even lower for ethnic minorities.[2] Teleretinal screening (TR) for DR is an imaging-based technology with the capability to screen exponentially more patients than conventional in-clinic examinations ever could. Large screening programs around the world have demonstrated TR's effectiveness in cost-efficiently detecting vision-threatening diabetic eye disease and improving screening compliance.[3-5]

Despite the tremendous potential of TR screening for DR, multiple challenges preclude its large-scale expansion at this time. Some of these include its limited accuracy in detecting diabetic macular edema,[3] prohibitive reimbursement rates, ambiguous medicolegal protections, and poor post-screening patient compliance. Recently, our group found that over a 4-year period, only 52.4% of patients screened in our TR program who were referred for an in-clinic exam actually attended.[6] Improving post-screening compliance and addressing the other aforementioned issues will be critical to the future success and feasibility of telemedicine screening for our diabetic patients.

In summary, TR screening for DR is a promising technology, especially with the incorporation of artificial intelligence, that could meaningfully reduce the prevalence of DR-associated vision loss. However, there are several obstacles that must first be overcome before TR screening for DR can be more widely implemented.

References

1. Huang ES, Basu A, O'Grady M, Capretta JC. Projecting the future diabetes population size and related costs for the U.S. *Diabetes Care*. 2009; 32(12):2225-2229.
2. Maclennan PA, McGwin G Jr, Heckemeyer C, et al. Eye care use among a high-risk diabetic population seen in a public hospital's clinics. *JAMA Ophthalmol*. 2014; 132(2):162-167.
3. Shi L, Wu H, Dong J, Jiang K, Lu X, Shi J. Telemedicine for detecting diabetic retinopathy: a systematic review and meta-analysis. *Br J Ophthalmol*. 2015; 99(6):823-831.
4. Ashman JJ, Talwalkar A, Taylor SA. Age differences in visits to office-based physicians by patients with diabetes: United States, 2010. *NCHS Data Brief*. 2014; 161:1-8.
5. Sharafeldin N, Kawaguchi A, Sundaram A, et al. Review of economic evaluations of teleophthalmology as a screening strategy for chronic eye disease in adults. *Br J Ophthalmol*. 2018; 102(11):1485-1491.
6. Date RC, Shen KL, Shah BM, Sigalos-Rivera MA, Chu YI, Weng CY. Accuracy of detection and grading of diabetic retinopathy and diabetic macular edema using teleretinal screening. *Ophthalmol Retina*. 2019; 3(4):343-349.

The Risk/Benefit Ratio for Brolucizumab Is Acceptable

Rishi P Singh MD

The Phase 3 HAWK and HARRIER studies demonstrated that brolucizumab, a novel single-chain antibody fragment anti-VEGF therapy, is noninferior to aflibercept in BCVA outcomes in patients with neovascular AMD (nAMD). In addition, there were statistically significant benefits in central subfield thickness and reductions of both intraretinal and/or subretinal fluid during the 96-week course of the trial. Slightly greater than 50% of patients were maintained on every 3-month dosing of brolucizumab during the first year of the study.

Since the time of drug release, a variety of safety events have been reported. The initial reports appeared in a American Society of Retina Specialists Research and Safety in Therapeutics (ReST) Committee report that demonstrated retinal vasculitis in 26 eyes, all treated with brolucizumab. Subsequently an independent safety review committee reported its findings after reviewing the HAWK and HARRIER dataset, demonstrating an overall rate of 4.6% with intraocular inflammation (IOI), 3.3% with IOI and retinal vasculitis, 2.1% with IOI and retinal vasculitis and retinal vascular occlusion, and less than 1% of patients experiencing a 15-letter vision loss along with IOI, retinal vasculitis, and retinal vascular occlusion. Interestingly the proportion of patients who experienced a 15-letter loss was equivalent in the aflibercept- and brolucizumab-treated groups within the study. This data was later confirmed with the IRIS® and KOMODO databases in more than 10,000 eyes, with numbers almost similar to those seen within HAWK and HARRIER.

Given these findings, is there a role for brolucizumab in the treatment of nAMD? The treatment burden of nAMD is high, with 40% of patients at intervals of less than every 8 weeks demonstrating persistent fluid and ongoing disease activity prior to the release of brolucizumab. Persistent fluid following treatment is also common, with over 50% of eyes demonstrating fluid despite being treated within a prospective clinical trial. Persistent fluid, especially early (less than 12 weeks), leads to long-term detrimental outcomes, and the data from HAWK and HARRIER supports improved outcomes, especially in these patients, over aflibercept, with a 5-letter difference in vision. Forty-six percent more patients within HAWK and HARRIER also gained 15 letters of vision on brolucizumab versus aflibercept. And we are aware that predictive factors, such as a prior history of IOI, can predict an event with brolucizumab.

Does brolucizumab have an acceptable risk/benefit ratio for patients? It depends. If your patient is doing exceedingly well with a low frequency of treatment and little residual fluid and good vision, there is no need to use brolucizumab. However, for the patient with frequent treatment intervals, residual fluid, high disease activity, no prior history of IOI, and loss of vision on current therapies, the risk/benefit ratio for brolucizumab is acceptable, and thus it has a role among the many drugs we have available for the treatment of nAMD.

Selected Readings

1. Dugel PU, Singh RP, Koh A, et al. HAWK and HARRIER: ninety-six-week outcomes from the phase 3 trials of brolucizumab for neovascular age-related macular degeneration. *Ophthalmology* 2021; 128(1):89-99.
2. Singh RP, Wykoff CC, Tadayoni R, et al. Visual and expanded anatomical outcomes for brolucizumab versus aflibercept in patients with neovascular AMD: 96-week data from HAWK and HARRIER. *Invest Ophthalmol Vis Sci*. 2019; 60(9);5194-5194.
3. Singh RP, Weichselberger A, Dugel PU. Comparative assessment of anatomical outcomes for nAMD patients treated with brolucizumab and aflibercept: 16-week data from the HAWK and HARRIER studies. *Invest Ophthalmol Vis Sci*. 2018; 59(9):1464-1464.
4. Singh RP, Hamilton R, Heier JS, et al. Disease activity assessments with brolucizumab vs aflibercept in patients with nAMD in HAWK and HARRIER. *Invest Ophthalmol Vis Sci*. 2020; 61(7):1158-1158.
5. Singer M, Albini TA, Seres A, et al. Clinical characteristics and outcomes of eyes with intraocular inflammation after brolucizumab: post hoc analysis of HAWK and HARRIER. *Ophthalmol Retina*. Epub ahead of print 2021 May 7. doi: 10.1016/j.oret.2021.05.003.
6. Monés J, Singh RP, Bandello F, Souied E, Liu X, Gale R. Undertreatment of neovascular age-related macular degeneration after 10 years of anti-vascular endothelial growth factor therapy in the real world: the need for a change of mindset. *Ophthalmologica* 2020; 243(1):1-8.
7. Singh RP, Yu JS, Agashivala N. Anti-VEGF treatment patterns in patients with wet age-related macular degeneration in clinical practice. *Ophthalmic Surg Lasers Imaging Retina*. 2021; 52(5):263-272.
8. Urbano CA, Maatouk C, Greenlee T, et al. Real-world treatment patterns in a population with neovascular AMD treated with anti-VEGF agents. *Ophthalmic Surg Lasers Imaging Retina*. 2021; 52(4):190-198.

The Risk/Benefit Ratio for Brolucizumab Is *Not* Acceptable

Paul Hahn MD PhD

Following the FDA approval of brolucizumab in October 2019, reports of associated adverse events emerged, including intraocular inflammation (IOI) with and without retinal vasculitis. Some of these cases were associated with significant and irrecoverable vision loss, and their features and outcomes have been documented in a growing body of post-marketing, real-world analyses. These events, particularly retinal vasculitis, were not well characterized in the initial analyses of the Phase 3 HAWK and HARRIER trials, but careful post hoc analysis has identified a rate of IOI of 4.6% (~1 in 22 eyes), associated vasculitis of 3.3% (~1 in 30 eyes), and associated occlusive vasculitis in 2.1% (~1 in 48 eyes). The rate of moderate vision loss (≥3 lines) was 0.74% (~1 in 135 eyes), and the rate of severe vision loss (≥6 lines) was 0.46% (~1 in 217 eyes). Despite impressive efforts by Novartis and the global retina community to better understand these events, their etiology and optimal treatment are still not understood. Although pivotal trials demonstrated a superior drying effect with brolucizumab compared to aflibercept, which has also been anecdotally reported in real-world experience, vision outcomes in the Phase 3 trials were comparable. Until providers are better able to predict and manage these events, the risk/benefit ratio for brolucizumab is *not* acceptable in the face of safer alternative therapies with comparable vision outcomes.

References

1. Baumal CR, Bodhagi B, Singer M, et al. Expert opinion on management of intraocular inflammation, retinal vasculitis, and/or vascular occlusion after brolucizumab treatment. *Ophthalmol Ret*. 2021; 5(6):519-527.
2. Baumal CR, Spaide RF, Vajzovic L, et al. Retinal vasculitis and intraocular inflammation after intravitreal injection of brolucizumab. *Ophthalmology* 2020; 127(10):1345-1359.
3. Bulirsch LM, Sabmannshausen M, Nadal J, et al. Short-term real-world outcomes following intravitreal brolucizumab for neovascular AMD: SHIFT study. *Br J Ophthalmol*. Epub ahead of print 2021 Apr 12. doi: 10.1136/bjophthalmol-2020-318672.
4. Enriquez AB, Baumal CR, Crane AM, et al. Early experience with brolucizumab treatment of neovascular age-related macular degeneration. *JAMA Ophthalmol*. 2021; 139(4):441-448.
5. Monés J, Srivastava SK, Jaffe GJ, et al. Risk of inflammation, retinal vasculitis, and retinal occlusion-related events with brolucizumab: post hoc review of HAWK and HARRIER. *Ophthalmology* 2021; 128(7):1050-1059.
6. Singer M, Albini TA, Seres A, et al. Clinical characteristics and outcomes of eyes with intraocular inflammation after brolucizumab: post hoc analysis of HAWK and HARRIER. *Ophthalmol Retina*. Epub ahead of print 2021 May 7. doi: 10.1016/j.oret.2021.05.003.
7. Witkin AJ, Hahn P, Murray TG, et al. Occlusive retinal vasculitis following intravitreal brolucizumab. *J Vitreoret Dis*. 2020; 4(4):269-279.
8. Witkin AJ, Hahn P, et al. Brolucizumab-associated intraocular inflammation in eyes without retinal vasculitis. *J Vitreoret Dis*. 2021, in review.

The Best Treatment for Severe Nonproliferative Diabetic Retinopathy Without Diabetic Macular Edema Is Regular Anti-VEGF Therapy

Diana V Do MD

NOTES

The Best Treatment for Severe Nonproliferative Diabetic Retinopathy Without Diabetic Macular Edema Is Regular Observation

Ramin Tadayoni MD PhD

I. Today there is no strong evidence that the available treatments can actually improve diabetic retinopathy beyond their impact on its indirect signs.

A. Anti-VEGF can improve Diabetic Retinopathy Severity Scale (DRSS) on color photos.

As expected from an effective anti-angiogenic agent, anti-VEGF drugs have been shown to be able to control new vessels in diabetic retinopathy eyes. It has also been shown that the DRSS on color fundus photos can improve after intravitreal injections of anti-VEGF.[1,2]

B. Color fundus photo signs are validated surrogates for estimating risk of proliferation in untreated eyes, but their value after injections has never been established.

Anti-VEGF intravitreal injections, as steroid injections, can clean the fundus from hemorrhages and signs of VEGF impregnation without eliminating risks of neovascularization shortly after discontinuation of the treatment.[3] This may indicate that the ischemia persists despite improvement of the fundus.

C. After anti-VEGF injections we did not find reperfusion of vessels despite DRSS improvement on color photos.

With ultrawide-field (UWF) color photography (Optos, California; Optos, Scotland, UK) and fluorescein angiography (FA) at baseline (M0) and 1 month after 3 monthly anti-VEGF injections (M3) for diabetic macular edema (DME) in consecutive naïve eyes, we showed that when the DRSS score improved by at least 1 stage in 61% of eyes, no reperfusion of arterioles or venules was observed in or around nonperfusion areas. Then, carefully evaluating retinal perfusion after 3 intravitreal injections of anti-VEGF with fluorescein angiography, we did not find reperfusion of vessels despite DRSS improvement on color photos.[4] With a similar method but this time using widefield OCT angiography (WF-OCTA) (PlexElite, Carl Zeiss Meditec, California, USA), we found that DRSS improved quickly (M3 or before) after anti-VEGF treatment by at least 1 stage in most of the eyes (80%), and new vessels, when present, regressed. However, OCTA with better precision proved that no reperfusion occurred, including at the capillary level.[5] Both our studies show that DRSS can improve with no reperfusion. This invalidates reliance on DRSS alone for grading nonproliferative diabetic retinopathy after intravitreal injections.

II. Today no solid proof exits that a treatment can prevent vision decrease in severe nonproliferative diabetic retinopathy.

A. It has been suggested that anti-VEGF can stop nonperfusion aggravation in diabetics.

A few studies have evaluated changes in vascular density in the macula, mainly, and have shown that anti-VEGF can stop changes in this parameter.[6] However, diabetic retinopathy affects even more the periphery beyond 8 mm from the macula, and the occurrence of proliferation even in case of preventive anti-VEGF therapy contradicts any solid prevention of aggravation of nonperfusion.[7]

B. A clinical trial suggests no benefit in term of vision for preventive anti-VEGF vs. regular observation with treatment when needed. Period.

The Protocol W Randomized Clinical Trial aimed to answer the exact question of this debate: "Does aflibercept treatment of moderate to severe nonproliferative diabetic retinopathy prevent vision-threatening complications and benefit visual acuity compared with sham treatment?" and their conclusion is clear: "Preventive treatment did not confer visual acuity benefit compared with observation plus aflibercept if complications developed."

III. Until a treatment shows a better benefit/risk ratio, the best treatment for severe nonproliferative diabetic retinopathy without DME remains regular observation.

Although the risks of anti-VEGF treatment are small, the costs are considerable. Even more importantly, it has no proven benefit compared to observation and treatment when needed, and the same goes for laser. Laser as a one-time treatment can have some indications in high-risk cases when regular observation may not be possible. For all others, today there is no base for discussion: the best treatment for severe nonproliferative diabetic retinopathy without DME is regular observation. All energies should then be concentrated on better estimating the risk of complication in these eyes with a new classification system to improve management and timely treatment with less burden.

References

1. Ip MS, Domalpally A, Sun JK, Ehrlich JS. Long-term effects of therapy with ranibizumab on diabetic retinopathy severity and baseline risk factors for worsening retinopathy. *Ophthalmology* 2015; 122(2):367-374.
2. Gross JG, Glassman AR, Jampol LM, et al.; Writing Committee for the Diabetic Retinopathy Clinical Research Network. Panretinal photocoagulation vs intravitreous ranibizumab for proliferative diabetic retinopathy: a randomized clinical trial. *JAMA* 2015; 314(20):2137-2146.
3. Wubben TJ, Johnson MW; Anti-VEGF Treatment Interruption Study Group. Anti-VEGF therapy for diabetic retinopathy: consequences of inadvertent treatment interruptions. *Am J Ophthalmol*. 2019; 204:13-18.
4. Bonnin S, Dupas B, Lavia C, et al. Anti-vascular endothelial growth factor therapy can improve diabetic retinopathy score without change in retinal perfusion. *Retina* 2019; 39(3):426-434.
5. Couturier A, Rey PA, Erginay A, et al. Swept-source wide-field OCT-angiography versus ultra-wide-field fluorescein angiography assessments of retinal non-perfusion in diabetic retinopathy and edema treated with anti-VEGF. *Ophthalmology* 2019; 126(12):1685-1694.
6. Alagorie AR, Nittala MG, Velaga S, et al. Association of intravitreal aflibercept with optical coherence tomography angiography vessel density in patients with proliferative diabetic retinopathy: a secondary analysis of a randomized clinical trial. *JAMA Ophthalmol*. 2020; 138(8):851-857.
7. Maturi RK, Glassman AR, Josic K, et al.; DRCR Retina Network. Effect of intravitreous anti-vascular endothelial growth factor vs sham treatment for prevention of vision-threatening complications of diabetic retinopathy: the Protocol W randomized clinical trial. *JAMA Ophthalmol*. Epub ahead of print 2021 Mar 30. doi: 10.1001/jamaophthalmol.2021.0606.

The Best Procedure for Large Refractory Macular Hole Is Autologous Retinal Transplantation

Dilraj S Grewal MD

Autologous retinal transplantation is the best procedure for large refractory macular holes because rather than mobilizing macular tissue movement, it bridges the gap by adding retinal tissue that integrates within the macular tissue and closes the hole. There is potential for alignment of neurosensory layers between the grafted retina and macular tissue along with reconstitution of the ellipsoid zone, both associated with better visual recovery. Vascularization of the graft has also been demonstrated. While recognizing that the procedure is not suitable in all cases and that with silicone-oil or short-term perfluorocarbon liquid tamponade there is a need for additional surgery for removal, there are data demonstrating a nearly 90% anatomical closure rate in large refractory macular holes, including those associated with retinal detachment, and nearly 40% of eyes show at least 3 lines of visual acuity gain.

Selected Readings

1. Grewal DS, Charles S, Parolini B, Kadonosono K, Mahmoud TH. Autologous retinal transplant for refractory macular holes: Multicenter International Collaborative Study Group. *Ophthalmology* 2019; 126(10):1399-1408.
2. Tabandeh H. Vascularization and reperfusion of autologous retinal transplant for giant macular holes. *JAMA Ophthalmol.* 2020; 138(3):305-309.
3. Moysidis SN, Koulisis N, Adrean SD, et al. Autologous retinal transplantation for primary and refractory macular holes and macular hole retinal detachments: the Global Consortium. *Ophthalmology* 2021; 128(5):672-685.

The Best Procedure for Large Refractory Macular Hole Is Perifoveal Hydrodissection

Carsten H Meyer MD for the SEAL Collaboration

Introduction

Most full-thickness macular holes (FTMHs) are closed by removing the underlying epiretinal pathology, including vitreous adhesions, internal limiting membrane (ILM), and adherent epiretinal membranes (ERM). This eliminates all centrifugal forces, so that the retracted elastic retina may relocate to its original position. Secondary attempts to close refractory FTMHs include additional installation of silicone oil, autologous platelet concentrates or ILM flap application to scaffold the MH, inducing centripetal force to readapt refractory MH. However, if refractory FTMHs fail, additional subretinal (SR) adhesions may play an important role in preventing the closure of a persisting MH (PMH). Known risk factors for PMH include large sized FTMH, long duration MH, traumatic MH, and FTMH in eyes with uveitis or drusen. In all these circumstances, secondary alterations may occur between the photoreceptors and retinal pigment epithelium (RPE), inducing firm adhesions between the neuroretina and adjacent the RPE-choriocapillaris complex, thus preventing the natural relocation of the retracted elastic neuroretina. In September 2002, during the Gonin Meeting in Montreux, Gonvers et al[1] presented SR fluid application in FTMHs. Many single-center groups described their technique in greater detail.

Recently, we evaluated in a first multicenter pilot study the feasibility and safety of this SR surgical approach among 12 VR surgeons. The APOSTEL study confirmed SR hydrodissection as a fast and reliable approach without a great learning curve or serious adverse events and determined an anatomical success in 35 of 41 refractory MHs, corresponding with a closure rate of 87.8% from a short-term perspective. Based on these encouraging surgical assessments, we evaluate here the patients' functional and additional anatomical long-term outcome in eyes with large or refractory MHs after this approach from 34 surgeons globally for a broader real-world perspective.

Methods

Thirty-four experienced VR surgeons from 31 participating centers reported their subretinal hydrodissection to close large full thickness macular holes for the SEAL collaboration. The final multicenter, retrospective, interventional, consecutive case series involved a total of 152 eyes from 152 consecutive patients who were diagnosed with large or refractory MH.

Technical approach and surgical considerations

Our modified technique was initially presented at the 2019 Vail vitrectomy meeting. A corresponding instructional video may be seen at the Academy website (www.aao.org/clinical-video/how-to-close-macular-hole-using-subretinal-fluid):

1. *Install a small heavy liquid perfluoro-n-octane (PFO) bleb* (2-3 DD) over the FTMH to cover the edges of the cuff. The purpose of this PFO bleb is to seal the MH, thus preventing an early antegrade draining of SR fluid from the SR space through the FTMH.
2. Place the *retinotomy in the mid distance between the edge of the MH* and the arcade of the upper or perpendicular lower arcade of the retinal vessels.
3. *Apply 3 small SR blebs* of 2-3 DD in the superior, temporal, and inferior quadrant using a 41-gauge SR cannula (Figure 1).
4. Once 2-3 SR blebs have created the intended SR detachment and stretching of the retina, *the sealing PFO bleb may be withdraw*n (Figure 2).
5. SR detachment will now expand toward the center and the PMH (Figure 3).
6. *Closure by a temporary endotamponade* gas application and posturing for 2-3 days is currently recommended (Figure 4).

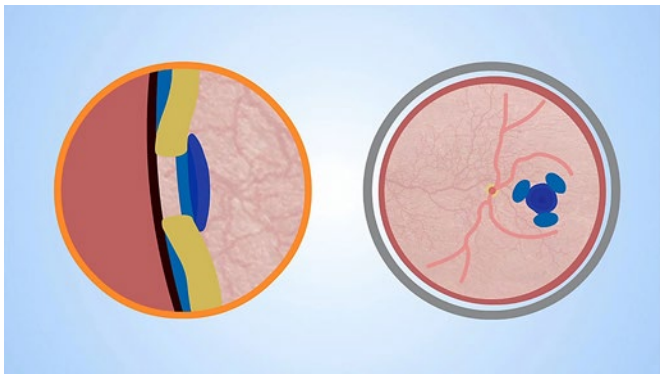


Figure 1

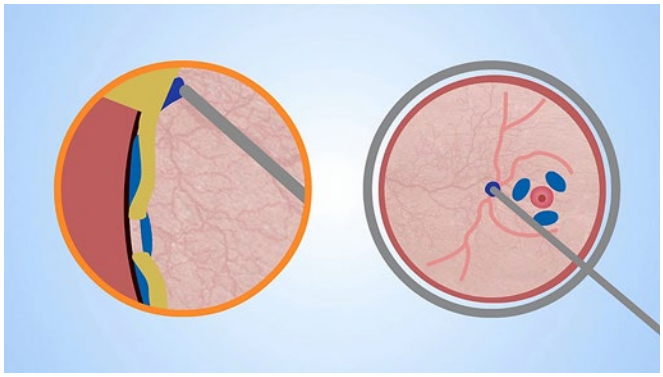


Figure 2

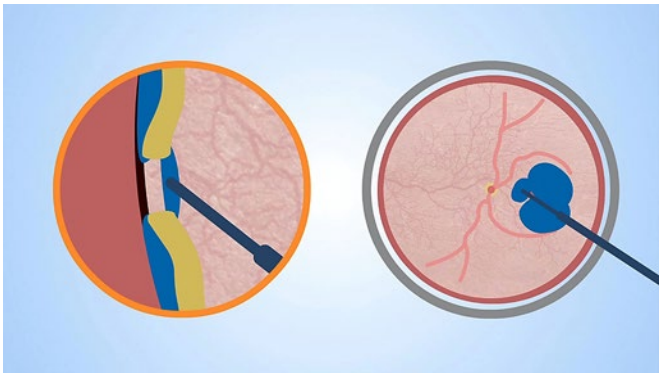


Figure 3

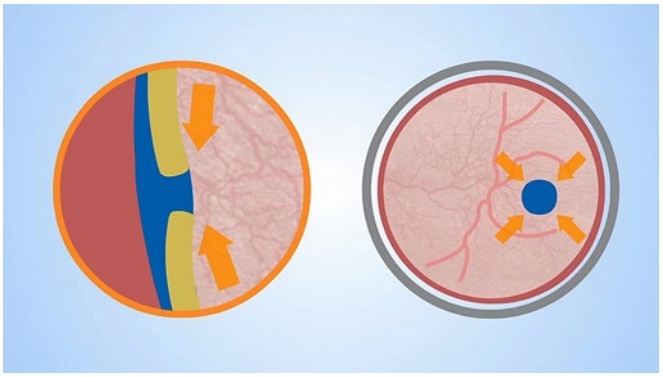


Figure 4

Results

Thirty-four VR surgeons from 31 centers and 13 countries contributed 152 consecutive surgeries performed on 152 eyes including Group 1: idiopathic MH (n = 119; 78.3%), Group 2: secondary MHs (n = 33; 21.7%).

Anatomic outcomes after SR fluid application

All 152 MHs received SR hydrodissection. Mean maximum diameter of all MHs was 1121 ± 482 µm, and the mean minimum MH diameter was 609.8 ± 269 µm, with a mean duration of 16.8 ± 11.9 months. There was an *83.6% MH closure rate* after SR hydrodissection (n = 127). The majority of the 127 closed MHs were idiopathic (n = 107, 85%). All closed MHs had a mean maximum MH diameter of 1082 ± 488 µm, duration 11.6 ± 11.9 months. All MHs up to a diameter of 521 µm closed completely after SR hydrodissection. The largest closed MH had a preoperative diameter of 4344 µm after SR fluid application.

Group 1 contained 119 idiopathic MHs after SR hydrodissection (78.3% of all MHs). Mean maximum MH diameter was 1097.4 ± 388 µm, and the mean minimum MH diameter was 585.5 ± 228.2 µm. There was an *89.9% MH closure rate* after SR fluid application (n = 107), 12 out of 119 idiopathic MHs remained open (10.1%). Ten of these 12 unclosed idiopathic MHs had a diameter greater 1055 µm (range: 1055-2670 µm), and 7 had a long-lasting duration, greater than 12 months (range: 12-240 months).

In Group 2 there were 33 cases of SR hydrodissection for secondary MHs (21.1% of all MHs). The diagnosis for secondary MH formation was high myopia > –6 dpt, n = 12; iatrogenic MH after ILM peeling, n = 7; after retinal detachment surgery, n = 6; vascular AMD, n = 3; after trauma, n = 2; drusen, n = 1; diabetic vitreomacular traction, n = 1; MacTel, n = 1. The mean maximum MH diameter was 1211.3 ± 691 µm, and the mean minimum MH diameter was 703.1 ± 356 µm. The mean duration of the MH was 9.6 ± 9 months. There was a *60.6% MH closure rate* after SR hydrodissection (n = 20), while 13 (39.4%) remained open (high myopia, n = 5; after retinal detachment, n = 4; M. Paget, n = 1; retinal aneurysm, n = 1; MacTel, n = 1; exudative AMD, n = 1).

The preoperative mean logMAR visual acuity of all 152 eyes was 1.16 ± 0.44 (Snellen equivalent of 0.10), which improved to 0.81 ± 0.40 (Snellen equivalent of 0.21) at 6-8 weeks postoperatively and improved significantly to 0.70 ± 0.44 (Snellen equivalent of 0.27) at the last follow-up visit. There were 25% of patients who experienced no significant improvement (< 3-line gain), 20.3% who gained 3-4 lines, and 54.7% who gained at least 5 lines at 6 months.

Discussion

Persisting, large, or long-lasting MHs have a reduced prognosis to close even after repeated epiretinal surgical approaches. In these eyes, a simple SR hydrodissection may release persisting SR adhesions and seal the MHs. Although this approach is not new, only a few case series are available. Here we present the first global multicenter trial on 152 cases. Our observed closure rate was above 80%, similar to smaller previous reports. All MHs up to a diameter of 521 µm closed completely after SR hydrodissection, although the technique was also capable of closing even much larger holes (> 2000 µm). The expected prognosis in idiopathic MHs is even better, as 9 out of 10 idiopathic MHs (Group 1) closed, while even 6 out of 10 secondary MHs (60.1%) with severe anatomical alteration responded also to SR hydrodissection.

The SEAL collaboration is the first multicenter trial of PMH treated with SR hydrodissection. Our surgical results confirmed easy and fast application, with minimal adverse events and a high surgical success rate. In agreement with previous case series, we observed within days a complete anatomical closure in more than 80% of cases. The physiologic elasticity of the retracted liberated retina could close even large holes with a greater aperture diameter and improvement in their central vision.

The majority of our clinically observed MHs have an idiopathic etiology, with an onset of several months and a diameter below 600 µm. We observed a successful anatomical closure in all these cases. Even persisting secondary MHs with severe anatomical damage responded unexpectedly well to a SR hydrodissection, assuming the important role of occult SR adhesions in MH surgery.

References

1. Gonvers M, Bovey EH, Wolfensberger TJ. A new surgical approach for the closure of stage 4 macular holes. 4. Meeting of the Jules Gonin; September 2002; Montreux, Switzerland
2. Oliver A, Wojcik EJ. Macular detachment for treatment of persistent macular hole. Ophthalmic Surg Lasers Imaging. 2011; 42:516-518.
3. Szigiato AA, Gilani F, Walsh MK, Mandelcorn ED, Muni RH. Induction of macular detachment for the treatment of persistent or recurrent idiopathic macular holes. *Retina* 2016; 36:1694-1698.

4. Meyer CH, Borny R, Horchi N. Subretinal fluid application to close a refractory full thickness macular hole. *Int J Retina Vitreous*. 2017; 3:44.
5. Ruban A, Lytvynchuk L, Zolnikova A, Richard G. Efficiency of the hydraulic centripetal macular displacement technique in the treatment of traumatic full-thickness macular holes. *Retina* 2019; 39:S74-S8310.
6. Claes CC. Internal repair of very large, myopic and recurrent macular holes by creation of a central retinal detachment and silicone oil tamponade. *Retina* 2019; 39:suppl 1:S72-S73.
7. Frisina R, Tozzi L, Sabella P, Cacciatori M, Midena E. Surgically induced macular detachment for treatment of refractory full-thickness macular hole: anatomical and functional results. *Ophthalmologica* 2019; 242:98-105.
8. Meyer CH. Application of subretinal fluid in refractory macular holes. Vail Vitrectomy meeting; 2019.
9. Meyer CH, Szurman P, Haritoglou C, et al. Application of subretinal fluid to close refractory full thickness macular holes: treatment strategies and primary outcome APOSTEL Study. *Graefes Arch Clin Exp Ophthalmol*. 2020; 258:2151-2161.
10. Zas M, Lasave AF, Alfano A, Saravia M. Surgical technique for approaching chronic or persistent macular holes: two case reports. *Am J Ophthalmol Case Rep*. 2020; 18:100692.
11. Meyer CH, Adamcova M, Rodrigues EB, Stanzel B, Koss MJ. Closure of persisting full thickness macular holes by subretinal fluid application: technical approach and surgical considerations. *Klin Monbl Augenheilkd*. 2021; 237(1):e1.

Late Breaking Developments, Part I

Moderator: Mark S Humayun MD PhD

Panelists: Kanishka T Jayasundera MD, Dante Pieramici MD, Shlomit Schaal MD PhD, and Elliott H Sohn MD

NOTES

Results From a Phase 2 Study of ADVM-022 Intravitreal Gene Therapy for Diabetic Macula Edema: The INFINITY Trial

and the Neovascular AMD (OPTIC) Trial

David S Boyer MD

The introduction of anti-VEGF intravitreal (IVT) therapies transformed the treatment of prevalent retinal conditions such as neovascular AMD (nAMD) and diabetic macular edema (DME), with many patients initially regaining and/or maintaining vision.[1,2] However, the chronic nature of these conditions and the relatively short IVT half-life of anti-VEGF agents means that regular disease assessments and ongoing IVT injections are required in order to prevent disease progression and to maintain anatomical and visual outcomes,[3] placing a considerable burden on the patient, on their caregivers, and on health care systems. This treatment burden contributes to the phenomenon of patients in clinical practice not always achieving the same positive visual acuity outcomes as observed within the protocol-driven registration studies.[4,5] These suboptimal outcomes are often associated with undertreatment due to nonadherence or nonpersistence with regimens suggested by clinical studies or the recommended product label dosing frequencies.[6]

Intermittent dosing of anti-VEGFs, because it does not provide sustained VEGF suppression, may result in fluctuations in retinal thickness. A recent post hoc analysis of the Comparison of AMD Treatment Trial (CATT) and the Inhibition of VEGF in Age-Related CNV (IVAN) trial showed that nAMD patients with the greatest degree of anatomical fluctuation had the poorest visual acuity outcomes and an increased risk of progression of fibrosis and geographic atrophy in the macular lesion.[7]

A single-injection IVT gene therapy that durably expresses intraocular anti-VEGF via a biofactory approach could reduce the need for repeated anti-VEGF injections and improve outcomes for patients with prevalent retinal conditions such as nAMD and DME. ADVM-022 is a novel gene therapy approach to treating prevalent retinal diseases. Designed via directed evolution, ADVM-022 utilizes a vector capsid specifically designed for IVT administration, AAV.7m8, and carries an aflibercept coding sequence under the control of a proprietary expression cassette. A single IVT injection of ADVM-022 has demonstrated long-term expression of aflibercept in nonhuman primates (NHP) out to 2.5 years.[8] ADVM-022 is currently under investigation in 2 clinical studies: OPTIC in nAMD patients and INFINITY in DME patients.

OPTIC (NCT03748784) is an ongoing, open-label, multisite, dose-finding Phase 1 clinical trial of ADVM-022 in treatment-experienced patients with nAMD ($N = 30$). Subjects received a single IVT injection of ADVM-022 of 2E11 vg/eye (Cohorts 2 and 3) or 6E11 vg/eye (Cohorts 1 and 4). In Cohorts 1 and 2, an oral steroid prophylaxis regimen was given for 13 days, starting 3 days before ADVM-022 injection, while in Cohorts 3 and 4, the steroid prophylaxis regime was modified to a 6-week regimen of steroid eyedrops. The primary objective of OPTIC is to assess the safety and tolerability of ADVM-022, and secondary objectives include evaluation of visual function and anatomic outcomes and the need for supplemental therapy with bolus IVT aflibercept over a 2-year period.

Safety and efficacy data are available from patients followed for a median of 88 and 68 weeks at the 2E11 vg/eye dose (C2 and 3, respectively) and 104 and 36 weeks at the 6E11 vg/eye dose (C1 and 4).

In OPTIC, ADVM-022 has demonstrated durability out to 2 years following a single, in-office IVT injection. Visual and anatomical outcomes remain stable or improve. Sixty percent of patients receiving the 2E11 dose remain supplemental injection-free beyond 1 year. Additionally, the aflibercept protein levels at the 2E11 dose were within the modeled therapeutic range and sustained out to at least 1 year, consistent with levels observed 4-6 weeks after an aflibercept injection.

All ADVM-022-related ocular adverse events (AE) were mild (80%) to moderate (20%) in OPTIC patients with wet AMD. There has been no clinical or fluorescein evidence of posterior inflammation; no vasculitis, retinitis, choroiditis, vascular occlusions, or endophthalmitis. At the 2E11 vg/eye dose, ocular inflammation was minimal and responsive to steroid eye drops; 87% of patients (13/15) have discontinued steroid eye drops.

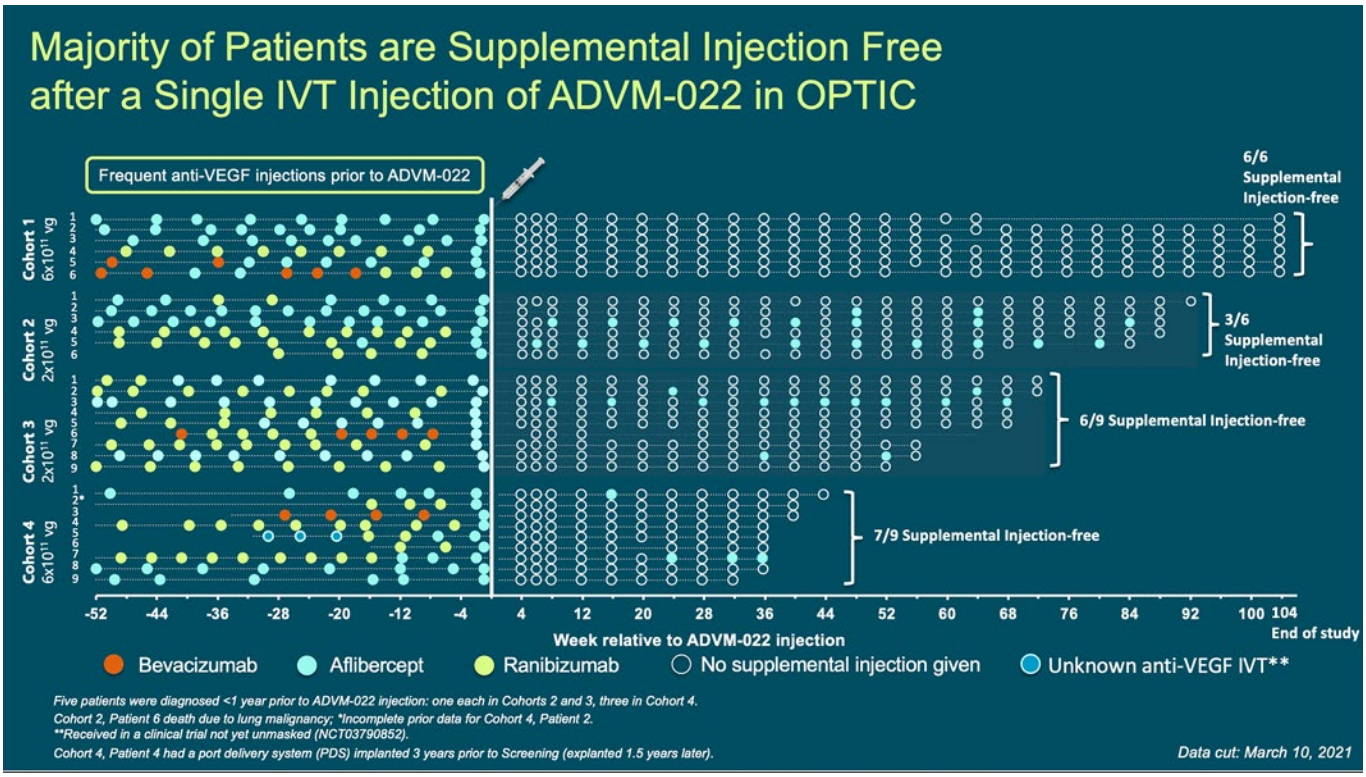


Figure 1. Reduction in number of IVT anti-VEGF injections required following ADVM-022 in OPTIC.

The INFINITY study (NCT04418427) is a Phase 2 multicenter randomized double-masked active comparator-controlled trial designed to assess a single IVT injection of ADVM-022 in patients with newly diagnosed DME (within 6 months of screening) that have received up to 2 prior injections of anti-VEGF therapy in the study eye ($N = 36$). Patients receive a single IVT injection of ADVM-022 2E11 vg/eye or 6E11 vg/eye or standard of care bolus IVT aflibercept and are evaluated monthly for 48 weeks. The primary endpoint is time to worsening of DME disease activity in the study eye. Incidence and severity of adverse events, change in visual acuity, change in central retinal thickness, and need for and number of supplemental aflibercept injections were evaluated. As of December 2020, the INFINITY study was fully enrolled.

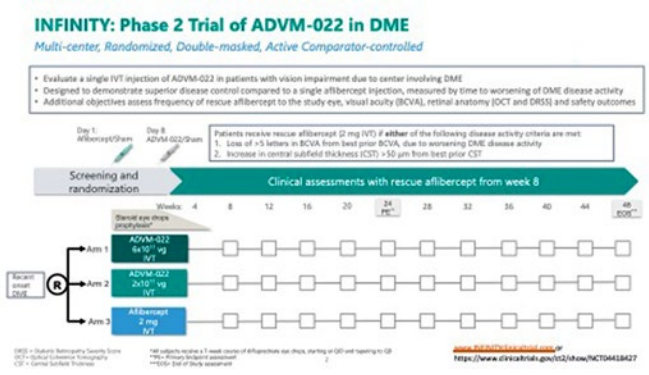


Figure 2. INFINITY study design.

Thirty weeks after a single IVT injection of 6E11 vg/eye, 1 patient experienced a suspected unexpected serious adverse reaction (SUSAR) of hypotony. This event was associated with panuveitis and loss of vision in the treated eye. Following this unexpected adverse event, the INFINITY study has been unmasked in order to analyze all data available and monitor every patient who has received gene therapy within the study. A thorough review of all the preclinical and clinical data from the ADVM-022 program is under way.

Conclusion

Despite advances in the treatment of prevalent retinal conditions, there still remain significant unmet medical needs. Gene therapy shows early promise in addressing these needs and warrants further investigation to more clearly elucidate mechanism of action, dose selection, and adverse event profile.

References

1. Rosenfeld PJ, Brown DM, Heier JS, et al. Ranibizumab for neovascular age-related macular degeneration. *N Engl J Med*. 2006; 355(14):1419-1431.
2. Heier JS, Brown DM, Chong V, et al. Intravitreal aflibercept (VEGF Trap-Eye) in wet age-related macular degeneration. *Ophthalmology* 2012; 119(12):2537-2548.
3. Niwa Y, Kakinoki M, Sawada T, Wang X, Ohji M. Ranibizumab and aflibercept: intraocular pharmacokinetics and their effects on aqueous VEGF levels in vitrectomized and nonvitrectomized macaque eyes. *Invest Ophthalmol Vis Sci*. 2015; 56(11):6501-6505.

4. Khanani AM, Skelly A, Bezlyak V, Griner R, Rodriquez Torres L, Sagkriotis A. SIERRA-AMD: a retrospective, real-world evidence study of patients with neovascular age-related macular degeneration in the United States. *Ophthalmol Retina*. 2020; 4(2):122-133.
5. Holz FG, Tadayoni R, Beatty S, et al. Multi-country real-life experience of anti-vascular endothelial growth factor therapy for wet age-related macular degeneration. *Br J Ophthalmol*. 2015; 99(2):220-226.
6. Okada M, Mitchell P, Finger RP, et al. Nonadherence or nonpersistence to intravitreal injection therapy for neovascular age-related macular degeneration: a mixed-methods systematic review. *Ophthalmology* 2021; 128(2):234-247.
7. Evans RN, Reeves BC, Maguire MG, et al. Associations of variation in retinal thickness with visual acuity and anatomic outcomes in eyes with neovascular age-related macular degeneration lesions treated with anti-vascular endothelial growth factor agents. *JAMA Ophthalmol*. 2020; 138(10):1043-1051.
8. Kiss S, Bender KO, Grishanin RN, et al. Long-term safety evaluation of continuous intraocular delivery of aflibercept by the intravitreal gene therapy candidate ADVM-022 in nonhuman primates. *Transl Vis Sci Technol*. 2021; 10(1):34.

Two-Year Results From the Subretinal RGX-314 Gene Therapy Phase 1/2a Study for the Treatment of nAMD and an Update on Suprachoroidal Trials

Robert L Avery MD

I. Background

A. Frequent ocular anti-VEGF injections are approved to treat neovascular AMD (nAMD) and have been shown to reduce the risk of blindness in clinical trials.

B. Real-world evidence shows that patients often lose visual acuity over time, and most believe this to be a consequence of noncompliance with high treatment burden of current anti-VEGF injections.[1,2]

C. RGX-314 is a single-gene therapy intervention utilizing an adeno-associated virus (AAV) vector, AAV8, designed to deliver a transgene for a soluble anti-VEGF Fab, with the goal of providing continuous anti-VEGF therapy.[3]

II. A Phase I/IIa multicenter, open-label trial evaluated 5 escalating dose levels of a single subretinal administration of RGX-314 in previously treated nAMD subjects with a demonstrated response to ranibizumab prior to RGX-314 delivery.

A. The 5 doses in order by cohort are $3x10^9$, $1x10^{10}$, $6x10^{10}$, $1.6x10^{11}$, and $2.5x10^{11}$ genome copies/eye.

B. The primary endpoint was safety through Week 26. Secondary endpoints were assessed out to 2 years, including BCVA, central retinal thickness (CRT), need for anti-VEGF injections after RGX-314 administration, ocular and nonocular adverse events (AEs), and RGX-314 aqueous protein level.

C. Anti-VEGF injections could be administered as needed, beginning 4 weeks after treatment and every 4 weeks thereafter per investigator's discretion if 1 or more of the criteria applied:

1. CNV-related increased, new, or persistent fluid
2. Vision loss of ≥5 letters associated with fluid
3. New ocular hemorrhage

D. Patients were encouraged to enroll in a long-term follow-up (LTFU) study to assess safety and efficacy for up to a total of 5 years after RGX-314 administration. Visits are scheduled every 6 months for the first year and then annually, and patient management is per physician discretion.

III. Results as of 1/22/2021

Cohorts 1-5 (C1-5) enrollment completed ($N = 42$). Updated data will be presented.

A. Safety

1. RGX-314 was well tolerated with 1 possibly drug-related serious AE, a significant decrease in BCVA.
2. Common ocular AEs in the study eye included postoperative conjunctival hemorrhage (69%), retinal pigmentary changes (83% of patients in Cohorts 3-5; 67% of all patients), postoperative inflammation (36%), retinal hemorrhage (26%), postoperative visual acuity reduction (17%), eye irritation (17%), and eye pain (17%).
3. There were no reports of clinically determined immune responses, drug-related ocular inflammation, or postsurgical inflammation beyond what is expected following routine vitrectomy.

B. BCVA

1. Mean improvement for Cohort 3 at 2 years was +14 letters, and +12 letters after 3 years.
2. Cohorts 4 and 5 showed stable vision of +1 letter and –1 letter, respectively, at 1.5 years.
3. The lower dosed groups, Cohorts 1 and 2, had mean changes of –6 letters and +1 letter, respectively, at 2 years.

C. CRT

1. Stable for Cohort 3 (+2 µm), Cohort 2 (+25 µm) and Cohort 1 (–34 µm) at 2 years.
2. Cohorts 4 and 5 remained stable at 1.5 years (–46 µm and –93 µm, respectively).

D. Anti-VEGF rescue injections

1. Cohort 3 patients had a 66.7% reduction in the mean annualized injection rate after 3 years compared to the 12 months prior to administration of RGX-314. Fifty percent of patients (3/6) remained anti-VEGF injection free over 3 years, and 67% (4/6) were injection free after 9 months.

2. Cohort 4 patients had a 58.3% reduction in the mean annualized injection rate after 1.5 years compared to the 12 months prior to administration of RGX-314. Seventeen percent of patients (2/12) remained anti-VEGF injection free over 1.5 years, and 42% (5/12) were injection free after 9 months.
3. Cohort 5 patients had an 81.2% reduction in the mean annualized injection rate after 1.5 years compared to the 12 months prior to administration of RGX-314. Sixty-four percent of patients (7/11) remained anti-VEGF injection free over 1.5 years, and 73% (8/11) were injection free after 5 months.

E. Aqueous RGX-314 protein level assessed at set timepoints following RGX-314 dosing
   1. Dose-dependent protein production at 1 month and 1 year for C1-5
   2. Cohort 3 demonstrated sustained protein production at 2 years.

F. Conclusions
   1. As of 1/22/21, RGX-314 remained generally well tolerated in 42 patients across 5 dose cohorts.
   2. Long-term, durable treatment effects out to 3 years show the potential for one-time administration of RGX-314 to provide sustained clinical outcomes, including stable to improved visual acuity and meaningful reduction in anti-VEGF injection burden, in the treatment of nAMD.
   3. These results have informed study design of pivotal trial program, with 2 planned studies to evaluate efficacy and safety of RGX-314 in patients with nAMD.

References

1. Ciulla TA, Hussain RM, Pollack JS, Williams DF. Visual acuity outcomes and anti-vascular endothelial growth factor therapy intensity in neovascular age-related macular degeneration patients: a real-world analysis of 49 485 eyes. *Ophthalmol Retina*. 2020; 4:19-30.
2. Maguire MG, Martin DF, Ying GS; CATT Research Group. Five-year outcomes with anti-vascular endothelial growth factor treatment of neovascular age-related macular degeneration: the Comparison of Age-related macular degeneration Treatments Trials. *Ophthalmology* 2016; 123(8):1751-1761.
3. Liu Y, Fortmann SD, Shen J, et al. AAV8-antiVEGFfab ocular gene transfer for neovascular age-related macular degeneration. *Mol Ther*. 2018; 26(2):542-549.

Treatment of Geographic Atrophy Secondary to AMD With Pegcetacoplan: Updates on the Randomized Phase 3 DERBY and OAKS Trials

Charles C Wykoff MD PhD

Background

Geographic atrophy (GA) is an advanced form of AMD. The prevalence of GA is projected to markedly increase over the next 2 decades.[1-3] GA lesion growth is progressive, constant, and irreversible, and lesions can impact nonsubfoveal and subfoveal regions. Loss of visual function accompanies lesion growth, whether nonsubfoveal or subfoveal.[4]

FILLY

The FILLY trial, a randomized, masked, Phase 2, sham-controlled study, evaluated the efficacy and safety of intravitreal pegcetacoplan, an inhibitor of complement C3 cleavage, in the treatment of GA secondary to AMD.[5] A total of 246 patients were randomized 2:2:1:1 to monthly or every other month (EOM) pegcetacoplan or monthly or EOM sham injection.

The primary endpoint was met, with pegcetacoplan reducing GA lesion growth as measured by fundus autofluorescence (FAF) by 29% and 20% in the monthly and EOM groups, respectively, as compared to sham ($P = .008$ and $P = .067$, respectively, vs. sham) at 12 months.[5] Serious adverse events in the study eye were reported in 4.7%, 2.5%, and 1.2% of patients in the pegcetacoplan monthly, pegcetacoplan EOM, and sham groups, respectively. Exudations were reported in 16% of patients in the monthly group; 6% of patients in the EOM group; and 1% of patients in the sham group at 12 months; overall, a history of exudation in the fellow eye and presence of a double layer sign at baseline in the study eye were associated with an increased rate of exudation development.[6]

DERBY and OAKS

DERBY and OAKS are randomized, Phase 3, double-masked, sham-controlled, 24-month studies evaluating the efficacy and safety of the C3 inhibitor pegcetacoplan in GA secondary to AMD.[7,8] Approximately 600 patients in each study have been randomized 2:2:1:1 to pegcetacoplan monthly, pegcetacoplan EOM, sham monthly, or sham EOM. The primary endpoint of each study is the change in total GA lesion area based on FAF at month 12.

References

1. Boyer DS, Schmidt-Erfurth U, van Lookeren Campagne M, Henry EC, Brittain C. The pathophysiology of geographic atrophy secondary to age-related macular degeneration and the complement pathway as a therapeutic target. *Retina* 2017; 37(5):819-835.
2. Colijn JM, Buitendijk GHS, Prokofyeva E, et al. Prevalence of age-related macular degeneration in Europe: the past and the future. *Ophthalmology* 2017; 124(12):1753-1763.
3. Wong WL, Su X, Li X, et al. Global prevalence of age-related macular degeneration and disease burden projection for 2020 and 2040: a systematic review and meta-analysis. *Lancet Glob Health*. 2014; (2)2:e106-116.
4. Holekamp N, Wykoff CC, Schmitz-Valckenberg S, et al. Natural history of geographic atrophy secondary to age-related macular degeneration: results from the prospective Proxima A and B clinical trials. *Ophthalmology* 2020; 127(6):769-783.
5. Liao DS, Grossi FV, El Mehdi D, et al. Complement C3 inhibitor pegcetacoplan for geographic atrophy secondar to age-related macular degeneration: a randomized Phase 2 trial. *Ophthalmology* 2020; 127(2):186-195.
6. Wykoff CC, et al. *Ophthalmology*. In press.
7. Study to compare the efficacy and safety of intravitreal APL-2 therapy with sham injections in patients with geographic atrophy secondary to age-related macular degeneration. ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/NCT03525600.
8. A study to compare the efficacy and safety of intravitreal APL-2 therapy with sham injections in patients with geographic atrophy secondary to age-related macular degeneration. ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/NCT03525613.

MERLIN: Results From the Phase 3a Trial of Brolucizumab in Patients With nAMD and Persistent Retinal Fluid

Arshad M Khanani MD

NOTES

Three-Year Results of the PALADIN Study of the Fluocinolone Implant for Diabetic Macular Edema

Visual and Anatomic Changes, Reduced Treatment Burden, and Safety Signals Associated With the 0.19-mg Fluocinolone Acetonide Implant in Patients With Persistent or Recurrent Diabetic Macular Edema

Michael Singer MD on behalf of the PALADIN Investigator Group

Purpose

The PALADIN Study is a U.S. 3-year observational Phase 4 study focused on safety outcomes in patients with center-involved diabetic macular edema (CI-DME) treated with the 0.19-mg fluocinolone acetonide (FAc; Iluvien) implant that releases a microdose (0.2 µg/day) of corticosteroid for up to 36 months following injection. The FDA label for this durable treatment option requires a prior steroid challenge to mitigate risk of uncontrolled IOP rise. This report provides the 3-year readout safety findings with 0.19-mg FAc implant in a prospectively enrolled real-world DME patient population in the United States.

Methods

The full analysis safety population includes 202 eyes from 159 patients enrolled with CI-DME that received 0.19-mg FAc and were followed for up to 36 months. Primary objectives included the predictive value of a prior steroid challenge in mitigating IOP-related events following FAc injection. Secondary endpoints for the 36-month completer group (n = 94 eyes) included BCVA outcomes, central subfield thickness (CST) outcomes, and supplemental treatments needed throughout the study. Subjects were followed at Day 1, Week 1, Month 2, and quarterly from Month 3 up to Month 36.

Results

159 patients with 202 study eyes were analyzed, including 36-month completer subgroup (n = 94 eyes). One hundred percent of patients had received previous DME treatments such as anti-VEGF, steroid, and laser. Overall baseline mean BCVA was 61.5 ± 16.67 letters (Snellen equivalent ~20/63) in all eyes and 62.3 ± 15.78 letters for 36-month completers. Mean time on study was 27.56 ± 10.99 months (all eyes) and 35.52 ± 0.49 months (36-month completers). Throughout the 36 months, BCVA was either maintained or improved over time. At Month 36, the 36-month completer subgroup showed a mean BCVA of 66.03 ETDRS letters and a mean change from baseline of +3.61 letters (P = .02). Through Month 36, treatment burden showed a 67.6% reduction in the median number of supplemental treatments yearly (3.4 treatments yearly before FAc vs. 1 treatment yearly after FAc); 24.53% of eyes were treatment free at 36 months. Time to supplementation among the eyes requiring additional treatment occurred at a median of 18.59 months. Reduction in CST was statistically significant from Day 7 after FAc implant and remained for all timepoints to Month 36 (P < .001).

In the safety population (n = 202), the mean baseline IOP prior to Fac was 14.95 ± 3.92 mmHg. Over 3 years, the mean IOP remained stable compared to baseline (at Month 36, change from baseline was +0.54 mmHg (P = .34). Mean peak change from baseline was +3.61 mmHg and was observed at Month 9 (P < .001). The rate of incisional IOP-lowering surgery was 2.97% (3/6 cases were due to neovascular glaucoma and unrelated to steroid-induced hypertension). 23.76% of eyes experienced an IOP elevation >25 mmHg, the majority of which occurred by 1.25 years. 10.89% of eyes experienced an IOP elevation >30 mmHg, the majority of which occurred by 1.5 years. This compares favorably to the FAME 3-year rate of 18.4%. 20.3% of eyes received IOP-lowering medication. The positive predictive value (PPV) can be defined as the likelihood that IOP will remain ≤25 mmHg following FAc if the IOP remained ≤25 mmHg on the prior steroid. The PPV value was 77.95% based on the Max observed IOP; the PPV value increased to 96.92% when using the last observed IOP measure.

Conclusions

In the 36-month analysis, the safety profile did not reveal any new concerns in a real-world setting. Approximately 97% of the full population maintained stable or manageable IOP without the need for surgical intervention. With fewer treatments, patients were able to maintain or improve vision and have significantly reduced CST at all time points. Approximately a quarter of the population remained rescue free following FAc.

Selected Readings

1. Campochiaro PA, Brown DM, Pearson A, et al. Long-term benefit of sustained-delivery fluocinolone acetonide vitreous inserts for diabetic macular edema. *Ophthalmology* 2011; 118(4):626-635. e2
2. Eaton A, Koh SS, Jimenez J, Riemann CD. The USER study: a chart review of patients receiving a 0.2 µg/day fluocinolone acetonide implant for diabetic macular edema. *Ophthalmol Ther.* 2019; 8(1):51-62.
3. Mansour SE, Kiernan DF, Roth DB, et al. Two-year interim safety results of the 0.2 µg/day fluocinolone acetonide implant for the treatment of diabetic macular oedema: the observational PALADIN study. *Br J Ophthalmol.* 2021; 105(3):414-419.

Novel OCT Findings

Caroline R Baumal MD

I. Background

A. OCT was initially developed as a combined effort between researchers at MIT and New England Eye Center in Boston, Massachusetts.

B. The purpose of OCT is to produce an "optical biopsy," where imaging details approach the level of histopathology without the need for tissue removal.

C. OCT has transitioned from a research device to become a standard retinal imaging tool that is indispensable for diagnosis and treatment of a wide variety of retinal disorders.

II. Milestones in OCT Development Over the Last 3 Decades

1991: Huang, Fujimoto, Puliafito, Schuman: landmark paper in *Science*[1]

1993: First prototype images of patients at New England Eye Center, Boston

1996: Technology transfer to Zeiss, OCT 1 production (100 A-scan/s, 10 µm resolution)

1999: OCT 2 production

2002: OCT 3 production (400 A-scans/sec, 10 µm resolution)

2004: Spectral domain (SD) OCT reported clinically (>20,000 A-scans/sec)

2006: SD-OCT systems commercially available

2012: 9+ SD-OCT systems worldwide

2014/5: OCT angiography (OCT-A) systems start to be available

III. Continued New OCT Findings

A. Technological advances

1. Hardware, software
2. Faster scanning speeds, more data
3. Better light sources, broader bandwidth→ increased axial resolution
4. Longer wavelength (ie, swept source)
5. Enhanced depth imaging (EDI) OCT
6. OCT angiography
7. Multimodal imaging
8. Disease progression software, machine learning

B. Operator advancement

1. Utilize the entire OCT image, en face OCT or scanning laser ophthalmoscopy, map, structural
2. Emphasis on greyscale structural OCT over false color scale
3. Multicenter collaborations

C. Newly identified retinal disorders

More recently characteristic OCT signs

1. ± disease specific
2. Terms may be descriptive, histopathologic, or related to disease mechanism.

a. Internal limiting membrane drape (typically used in MacTel type 2)

b. Shallow irregular RPE (retinal pigment epithelium) elevation (SIRE), also referred to as double layer sign

c. Complete RPE and outer retinal atrophy (cRORA), incomplete RPE and outer retinal atrophy (iRORA)—Classification of Atrophy Meeting group definitions

d. Subretinal hyperreflective material (SHRM)

e. Flying saucer sign

f. Dome shaped macula

g. Disorganization of retinal inner layers (DRIL)

h. Bacillary detachment

i. Hyperreflective spots (HRS)

j. Outer retinal tubulation (ORT)

k. Outer retina-choroid complex (ORCC) splitting

l. Brush border pattern or elongation of PR outer segment

m. Peripapillary hyperreflective ovoid mass-like structures (POHMS)

n. Concentric macular rings (CMR)

o. Sponge sign in inflammatory CNV

p. Hump in myopia

q. RPE aperture

r. Henle layer hyperreflectivity

s. Henle hemorrhage (HH)

t. Focal ellipsoid loss

u. Pearl necklace sign

v. Foveal pseudocyst
w. Focal choroidal excavation (FCE)
x. Choroidal macrovessel
y. Choroidal caverns
z. Choroidal rift
a'. Pachychoroid/peripapillary pachychoroid syndrome
b'. Dipping sign
c'. Plume
d'. Fuzzy border
e'. Cotton ball sign
f'. Needle sign
g'. Dimple in vascularized PED

IV. Summary: OCT Technology and Knowledge Are Dynamic
A. The OCT ceiling has not been reached.
B. OCT biomarkers for disease and therapy

Reference

1. Huang D, Swanson EA, Lin CP, et al. Optical coherence tomography. *Science* 1991;254:1178-1181.

Other readings are numerous and available on request.

OCT Imaging of the Retinal Periphery

Netan Choudhry MD

Course Outline

I. Introduction

II. Brief Overview of History of Retinal Imaging for the Peripheral Retina

- A. Direct and indirect ophthalmoscopy
- B. Fundus photography
- C. Ultrawide-field imaging

III. Widefield and Ultrawide-Field Consensus Definition

International widefield imaging consensus

IV. Techniques for Imaging the Retinal Periphery

- A. Seven standard fields
- B. Navigated imaging
- C. Image montage
- D. Steered imaging
- E. New modalities

V. Utility of Imaging the Retinal Periphery in Clinical Practice

- A. Current review of data
- B. Observations by pathology
  1. Retinal tufts
  2. Retinal holes
  3. Lattice degeneration
  4. Retinal detachment(s)
  5. Choroidal lesions
  6. How to manage? (ie, are anti-VEGF injections gold standard?)
  7. Is there an association between NVAMD and CEIOL?
  8. Preoperative or perioperative management/ treatment with injections?
- C. Integrating peripheral retinal imaging in clinical practice

VI. Conclusions

Macrophages Swarming the Macula: Visualizing Cellular Activities in Retinal Vascular Disease Using Clinical OCT Imaging

Richard B Rosen MD

- Macrophages respond to cellular injury in the retina and play an important role in immunosurveillance, maintenance of media clarity, and regulation of vasculature.
- They are named according to their region of residence: hyalocytes along the vitreoretinal surface, or microglia within the retinal stroma.
- While most of our knowledge of their activities comes from animal models, recently adaptive optics OCT has been used to study these cells in vivo.
- Using commercial OCT, Castanos et al first demonstrated the ability to image these cells and map their distribution throughout the macula.

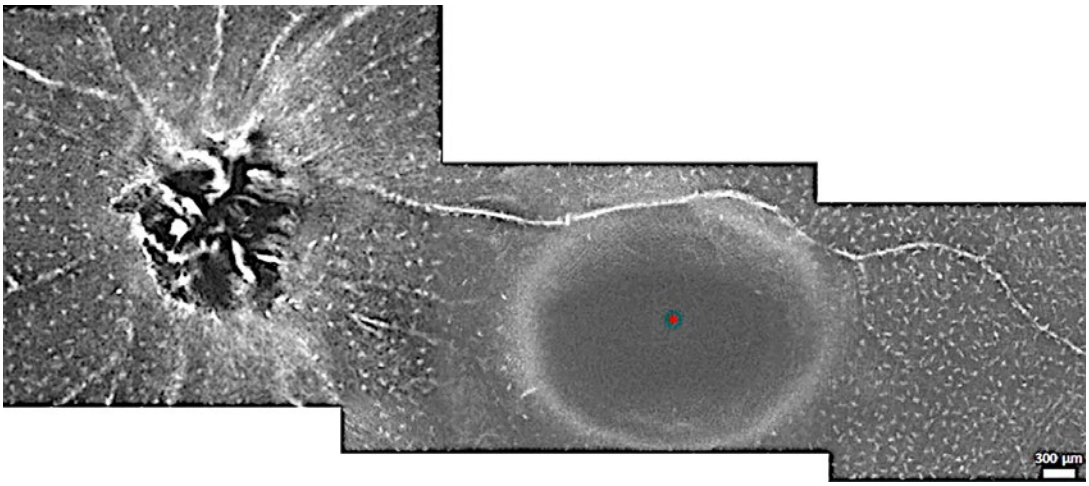


Figure 1. Macular montage of 3-µm en face OCT slabs acquired above the internal limiting membrane surface.

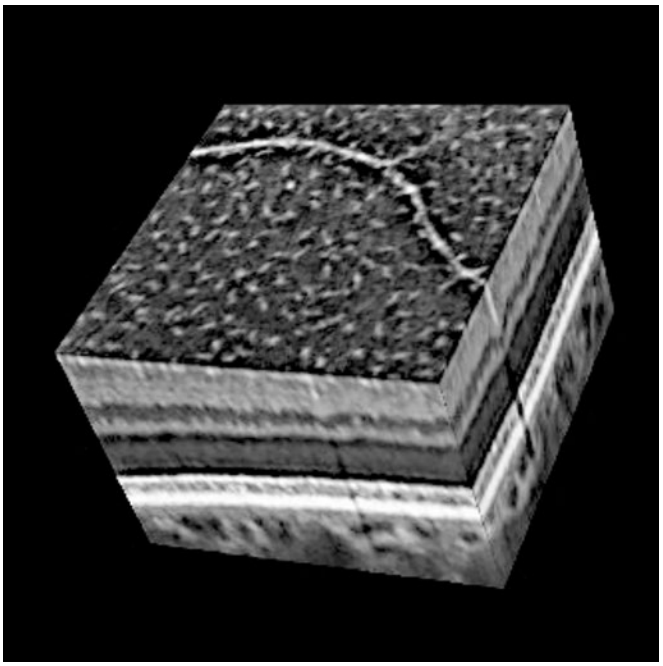


Figure 2. Cells at the vitreoretinal interface.

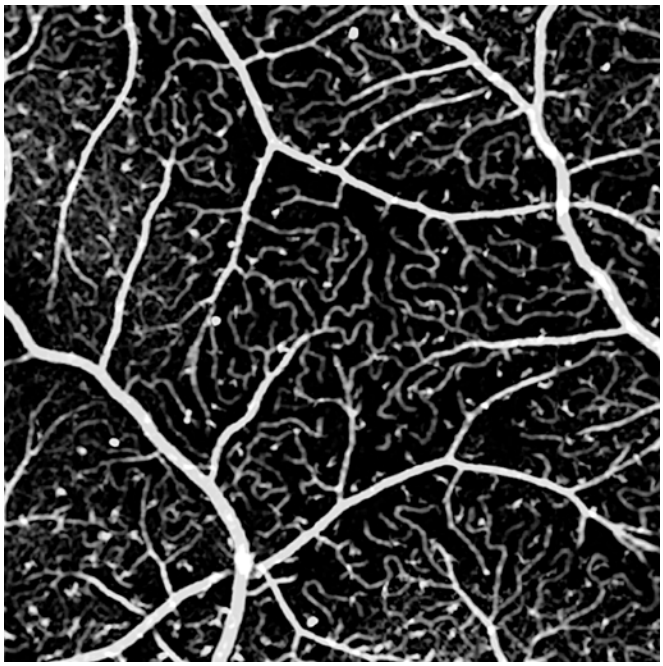


Figure 3. En face OCT overlaid on OCT angiography.

- These cells change in morphology and distribution in response to various retinal injuries. Patterns of cellular migration such as clustering at the macula and around blood vessel can be mapped with clinical OCT.
- Morphological alteration from inactive ramified forms to activated plumper shapes with fewer processes are best revealed by adaptive optics scanning laser ophthalmoscopy imaging (below).

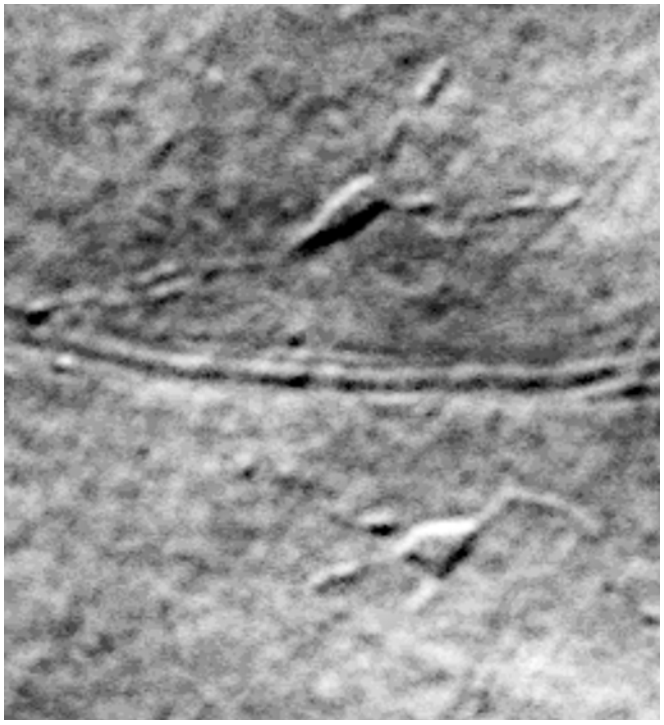


Figure 4. Resting surface macrophage from control.

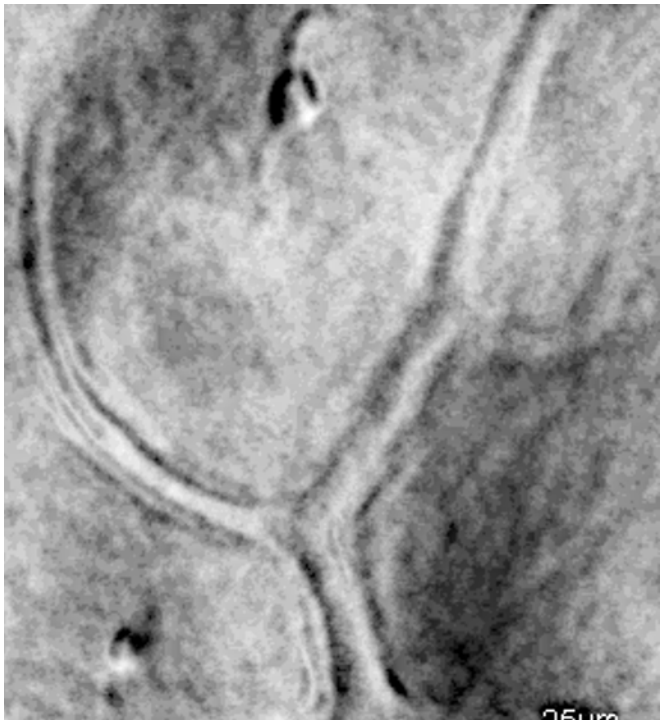


Figure 5. Plumper activated cells with fewer processes in diabetic patient.

- Retinal cellular imaging using clinical OCT could offer a level of diagnostic granularity unavailable with current imaging strategies.
- Surface macrophages could become a valuable therapeutics biomarker.

Selected Readings

1. Balazs EA, Toth LZ, Eckl EA, Mitchell AP. Studies on the structure of the vitreous body: XII. Cytological and histochemical studies on the cortical tissue layer. *Exp Eye Res*. 1964; 3:57-71.
2. Vagaja NN, Chinnery HR, Binz N, et al. Changes in murine hyalocytes are valuable early indicators of ocular disease. *Invest Ophthalmol Vis Sci*. 2012; 53:1445-1451.
3. Sakamoto T, Ishibashi T. Hyalocytes: essential cells of the vitreous cavity in vitreoretinal pathophysiology? *Retina* 2011; 31:222-228.
4. Liu Z, Kurokawa K, Zhang F, Lee JJ, Miller DT. Imaging and quantifying ganglion cells and other transparent neurons in the living human retina. *Proc Natl Acad Sci U S A*. 2017; 114:12803-12808.
5. Castanos MV, Zhou DB, Linderman RE, et al. Imaging of macrophage-like cells in living human retina using clinical OCT. *Invest Ophthalmol Vis Sci*. 2020; 61(6):48.
6. Hammer DX, Agrawal A, Villanueva R, Saeedi O, Liu Z. Label-free adaptive optics imaging of human retinal macrophage distribution and dynamics. *Proc Natl Acad Sci U S A*. 2020; 117(48):30661-30669.

Visualization of Posterior Vitreous by Ultrawide-field and AI-Based 3-D OCT Imaging

Kyoko Ohno-Matsui MD, Zaixing Mao, Hiroyuki Takahashi

Introduction

The vitreous, a gel-like structure that occupies four-fifths of the volume of the eye,[1,2] undergoes distinctive changes during normal aging and also under various pathological conditions. The pathologies include vitreomacular traction, proliferative vitreoretinopathy, and myopic macular retinoschisis. The pathological changes of vitreous can play important roles in the development of pathology in other intraocular tissues.

Imaging the vitreous in vivo is very difficult because it is a transparent structure and is generally not visible. Because the vitreous is difficult to observe, it has been analyzed mainly by histological examinations of autopsied eyes.[3-5] These histological studies revealed important aspects of the human vitreous, such as the presence of premacular bursa, internal cavities, and small cisterns within the vitreous. However, a noninvasive imaging method would reduce the artifactual damage to the vitreous structure that occurs during the dissection and preparation of the vitreous to make histological sections.

In addition, it is important to notice that vitreous acts as a large and constantly moving mass when it exerts tractional force. Thus, even when vitreous is observed in a single B-scan image, the scan shows a cross-sectional image of the vitreous that exists there at that moment. To overcome these concerns and to clarify how vitreous acts as a mass, it is necessary to visualize the entire figure of vitreous gel in three dimensions.

3-D Visualization of the Entire Vitreous Gel by Swept Source OCT

Swept source OCT (SS-OCT) instruments have much higher resolution than conventional OCT instruments. SS-OCT uses a long wavelength laser in the 1-micron range, and because of its lower roll-off sensitivity with tissue depth, it is suitable for imaging thicker tissues from the vitreous to the choroid and sclera. SS-OCT has contributed significantly to the information about the vitreous body, as was shown in the observation of the entire structure of the posterior precortical vitreous pocket (PPVP) in vivo.[6] To improve the viewing of the vitreous by SS-OCT, Spaide developed a technique that uses dynamic focusing and windowed averaging.[7]

Methodologies

Vitreous structures are difficult to observe in single OCT B-scan images because of the presence of speckle noise. In order to enhance the visualization of vitreous fluid space in 3-D OCT scans, a deep learning–based noise reduction algorithm, developed by Mao et al,[8] is applied to reduce the noise in each individual B-scan.

The labeling of vitreous fluid space is performed semiautomatically (Figure 1). First, from a 3-D OCT volume, vitreous fluids are manually labeled in representative 2-D OCT images along the axial, coronal, and sagittal planes. Next, based on said manual labels, a deep convolutional neural network is trained to interpolate the vitreous fluid locations for locations without manual labels. Finally, vitreous pocket labels generated from all 3 planes are combined together for manual inspection and correction. Using this technology, 3-D structure of vitreous fluid space is clearly shown (Figure 2).

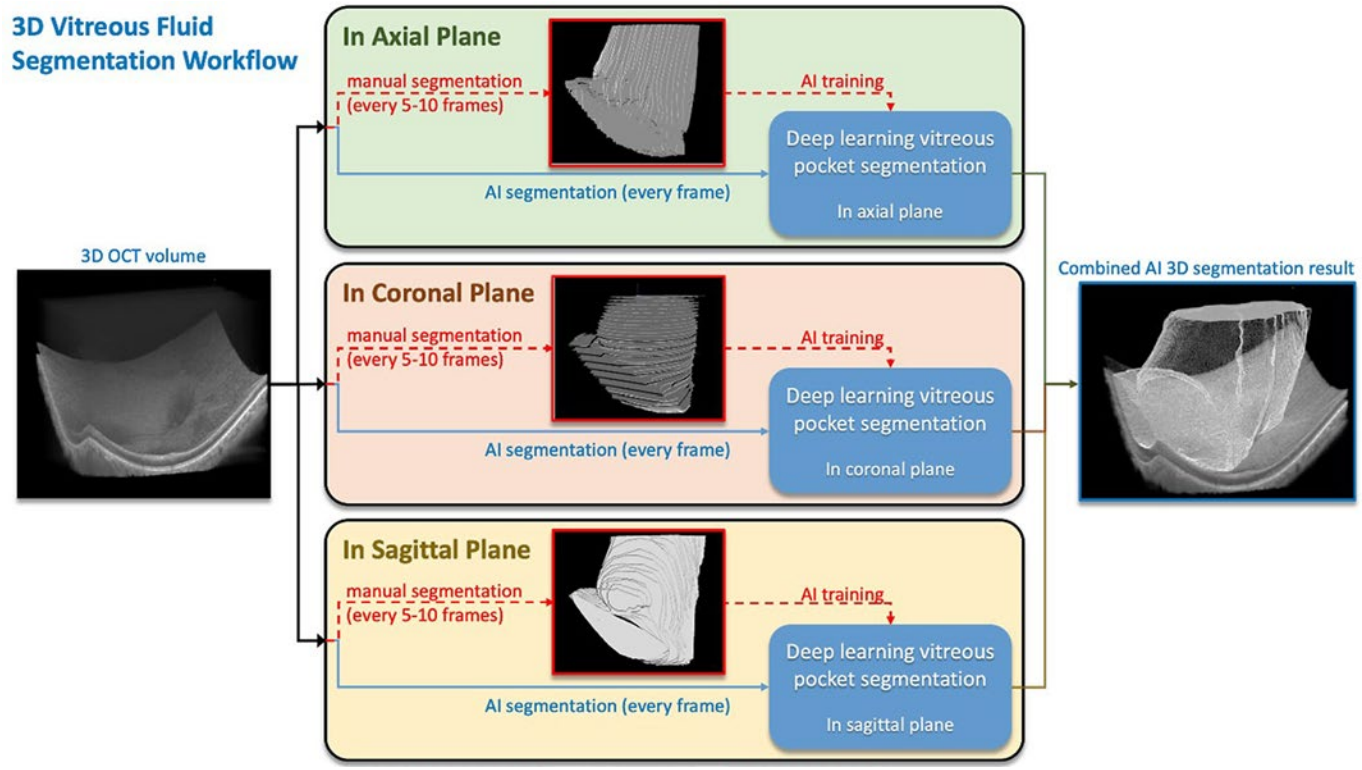


Figure 1

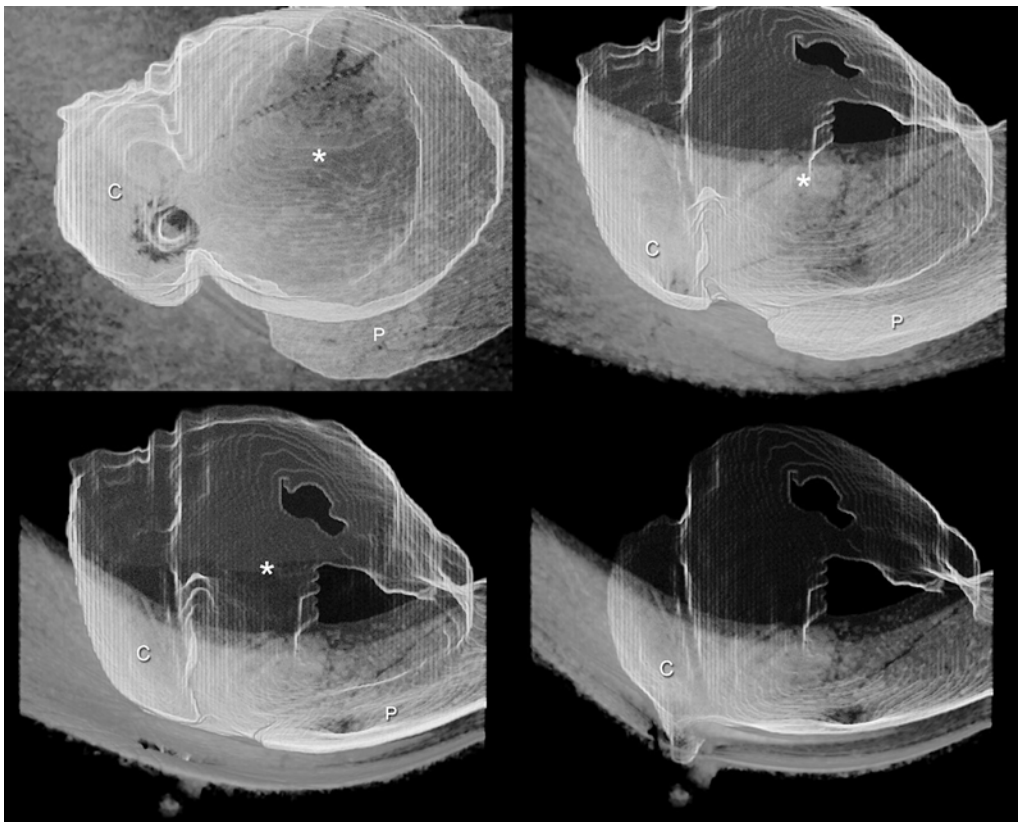


Figure 2

The spatial relationship between the PPVP, Cloquet canal, and other cisterns are clearly visible in a 3-D way. 3-D reconstructed images showed that the cisterns joined the PPVP and subsequently a wide channel went further upward. Multicolor images more clearly showed the relationship of various fluid spaces.

3-D Vitreous Visualization in Various Vitreoretinal Diseases

In addition to observing changes according to normal aging and myopization, vitreous structures were also observed in various vitreoretinal diseases, such as macular hole, retinal detachment, and proliferative diabetic retinopathy. Besides vitreous fluid space, vitreous gels surrounding the fluid as well as the vitreoretinal interface were also visualized by semiautomatic segmentation (Figure 3).

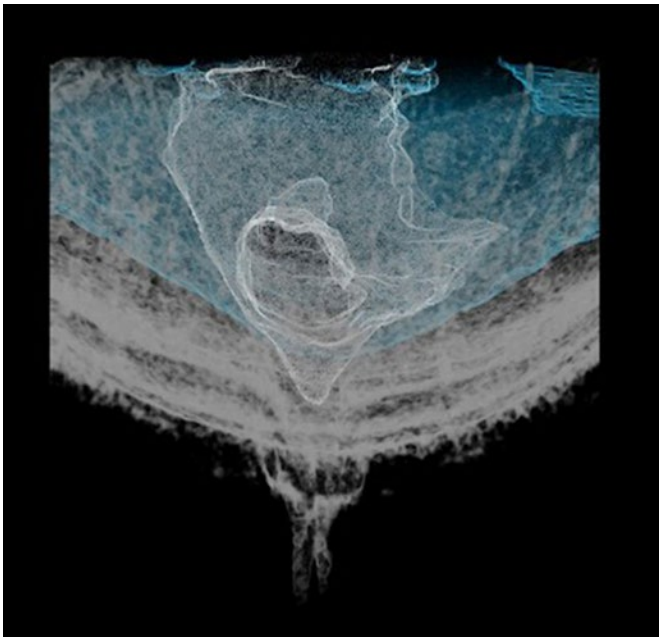


Figure 3

Conclusions

The vitreous may be one of the most difficult ocular tissues to image in vivo because it is a large and moving tissue. 3-D reconstruction of the entire figure of vitreous gel may meet this challenge, and we predict that this technique will provide new and effective information on the pathogenesis of various vitreoretinal disorders.

References

1. Hogan MJ, Alvarado JA, Weddell JE. The vitreous. In: Hogan MJ, Alvarado JA, Weddell JE, eds. *Histology of the Human Eye*. Philadelphia: WB Saunders; 1971:607-637.
2. Sebag J. *The Vitreous: Structure, Function, and Pathobiology*. New York: Springer-Verlag; 1989.
3. Eisner G. [Postmortem slitlamp study of the vitreous body: 3. Relation to histology, biomicroscopy and clinical applications]. *Graefes Arch Clin Exp Ophthalmol*. 1971; 182:23-40.
4. Worst JG, Los LI. Comparative anatomy of the vitreous body in rhesus monkeys and man. *Doc Ophthalmol*. 1992; 82:169-178.
5. Kishi S, Shimizu K. Posterior precortical vitreous pocket. *Arch Ophthalmol*. 1990; 108:979-982.
6. Kishi S. Impact of swept source optical coherence tomography on ophthalmology. *Taiwan J Ophthalmol*. 2016; 6:58-68.
7. Spaide RF. Visualization of the posterior vitreous with dynamic focusing and windowed averaging swept source optical coherence tomography. *Am J Ophthalmol*. 2014; 158:1267-1274.
8. Mao Z, Miki A, Mei S, et al. Deep learning based noise reduction method for automatic 3D segmentation of the anterior of lamina cribrosa in optical coherence tomography volumetric scans. *Biomed Opt Express*. 2019; 10:5832-5851.

How to Determine Posterior Vitreous Detachment Status With a 10-Second Retinal Nerve Fiber Layer Scan and Patient Age

David M Brown MD, Stephen M Laswell BS, Ankoor Shah MD, and Charlie Wykoff MD PhD (Retina Consultants of Texas, Houston, Texas, USA; Retina Consultants of America)

I. Posterior vitreous detachment (PVD) status is *critical* for vitreomacular interface disease management and surgical planning

A. El Bayadi lens/Goldmann lens

B. Ultrasound (B-scan)

C. PVD observation using OCT (Uchino, 2001)

II. Methods

A. 2002 eyes analyzed with Heidelberg OCT 2 retinal nerve fiber layer (RNFL) scan and macular volume scan

B. 3 masked graders with adjudication until 100% agreement

C. 2000/2002 eyes (99.9%) could be classified.

III. Distinct Stages Identified

Stage A. No RNFL separation (with or without partial vitreomacular separation)

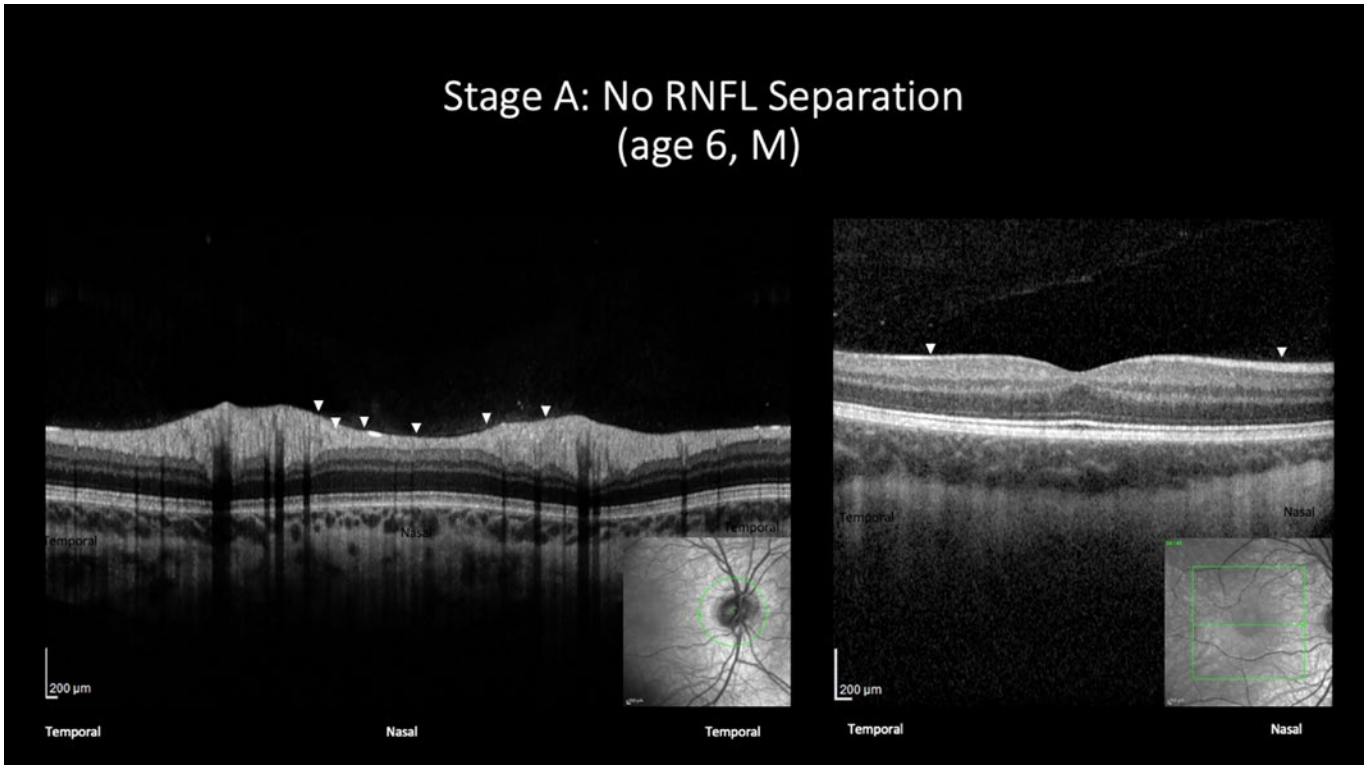


Figure 1

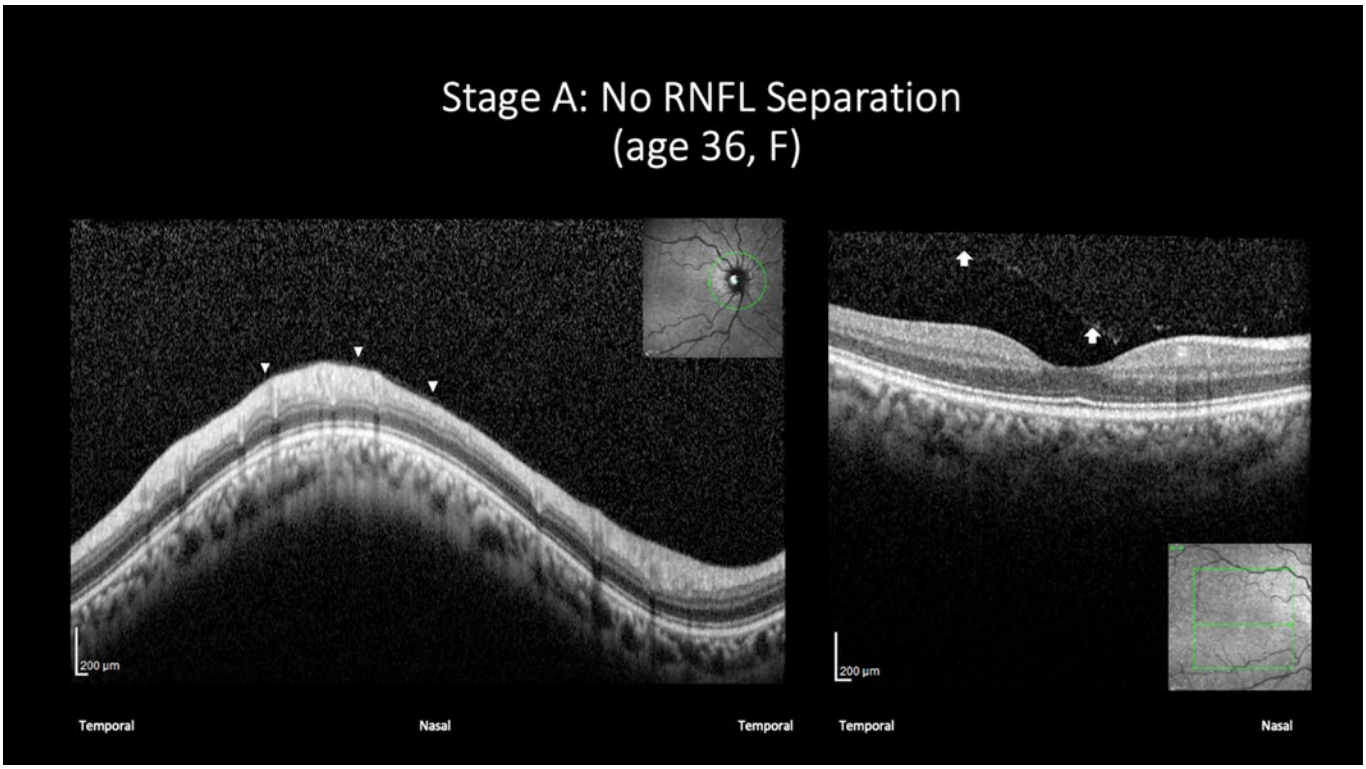


Figure 2

Stage B. Lamellar RNFL separation

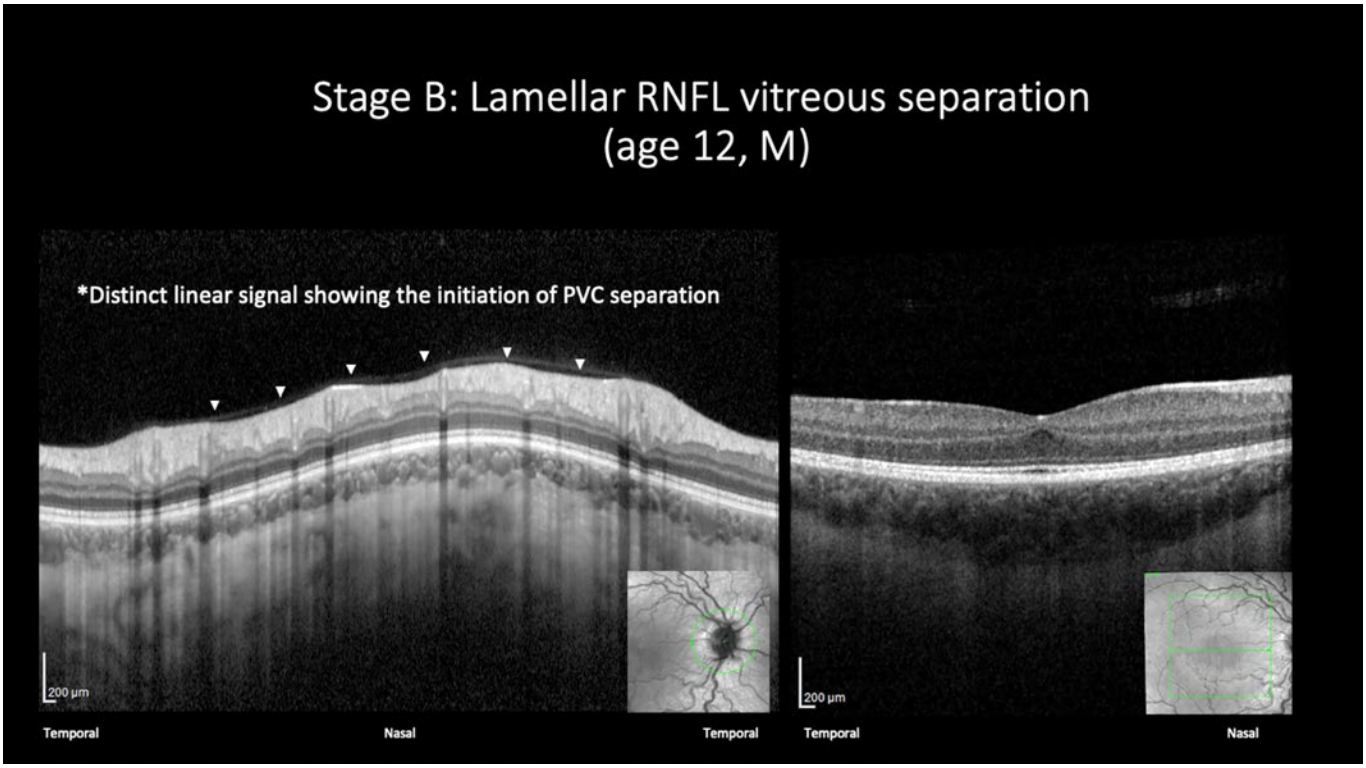


Figure 3

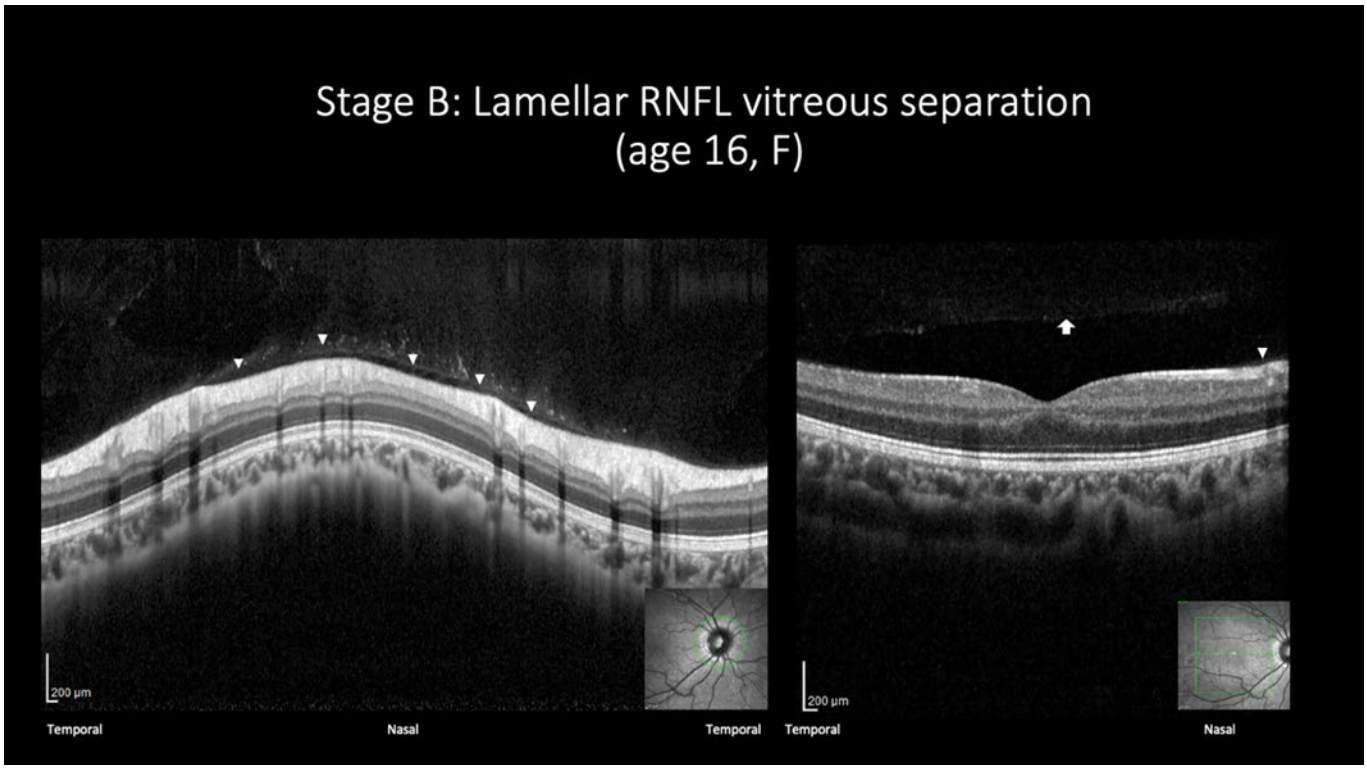


Figure 4

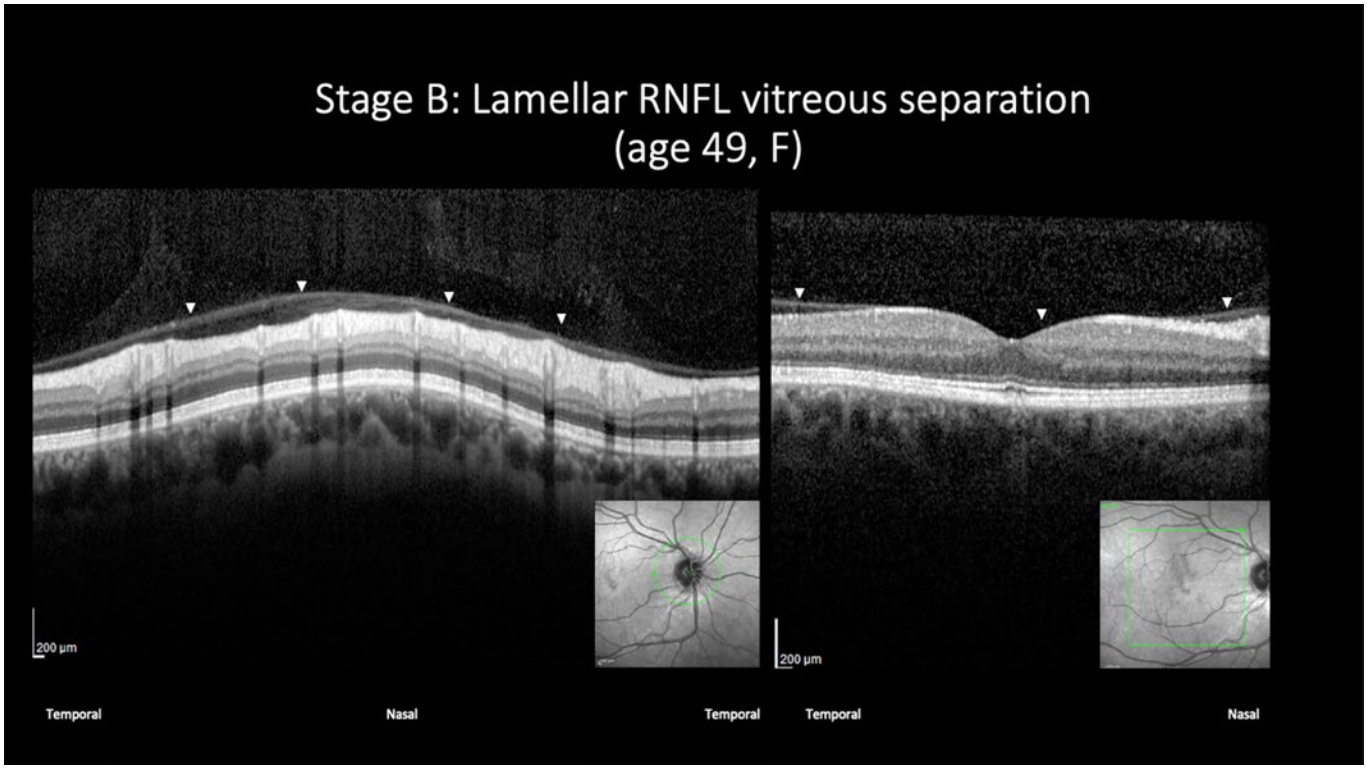


Figure 5

Stage C. Papillomacular bundle RNFL separation, complication stage! Note: In every case vitreopapillary adhesion is confirmed on volume scan over optic disc.

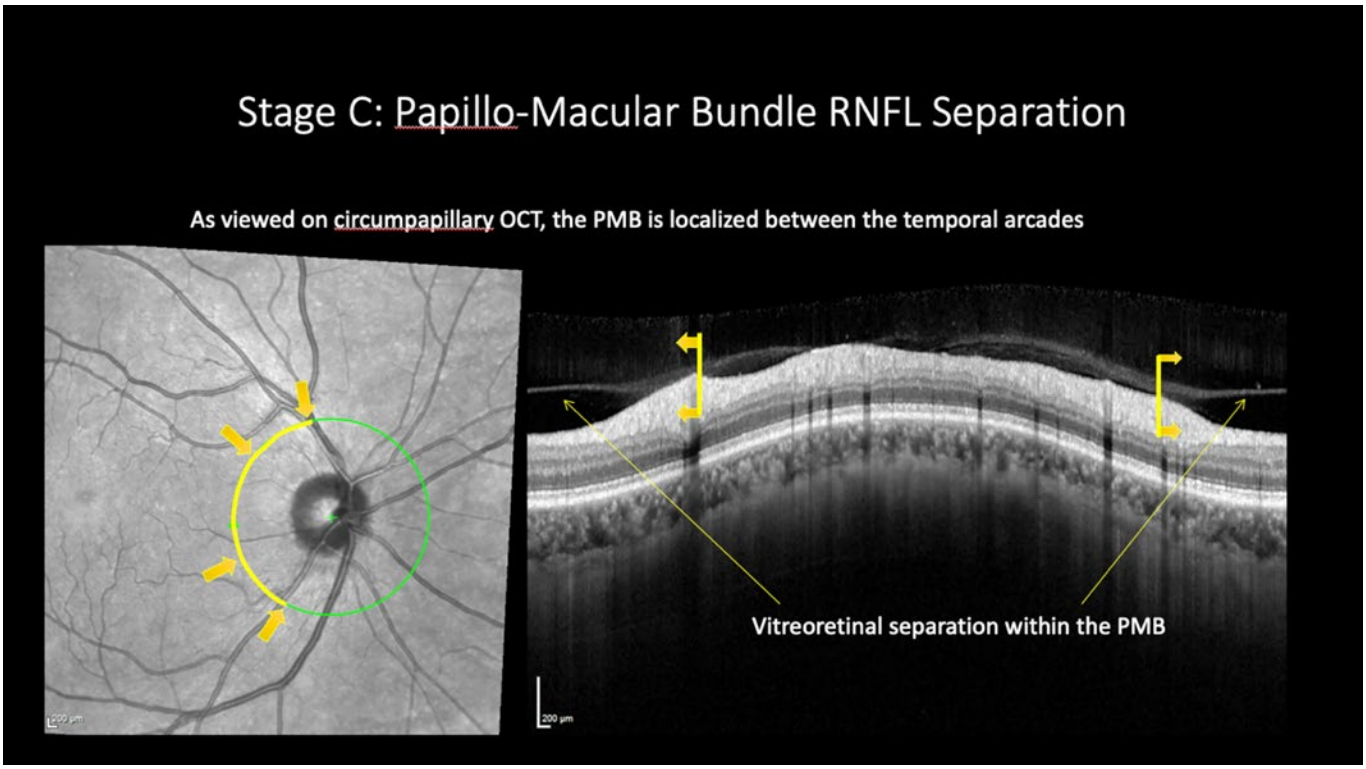


Figure 6

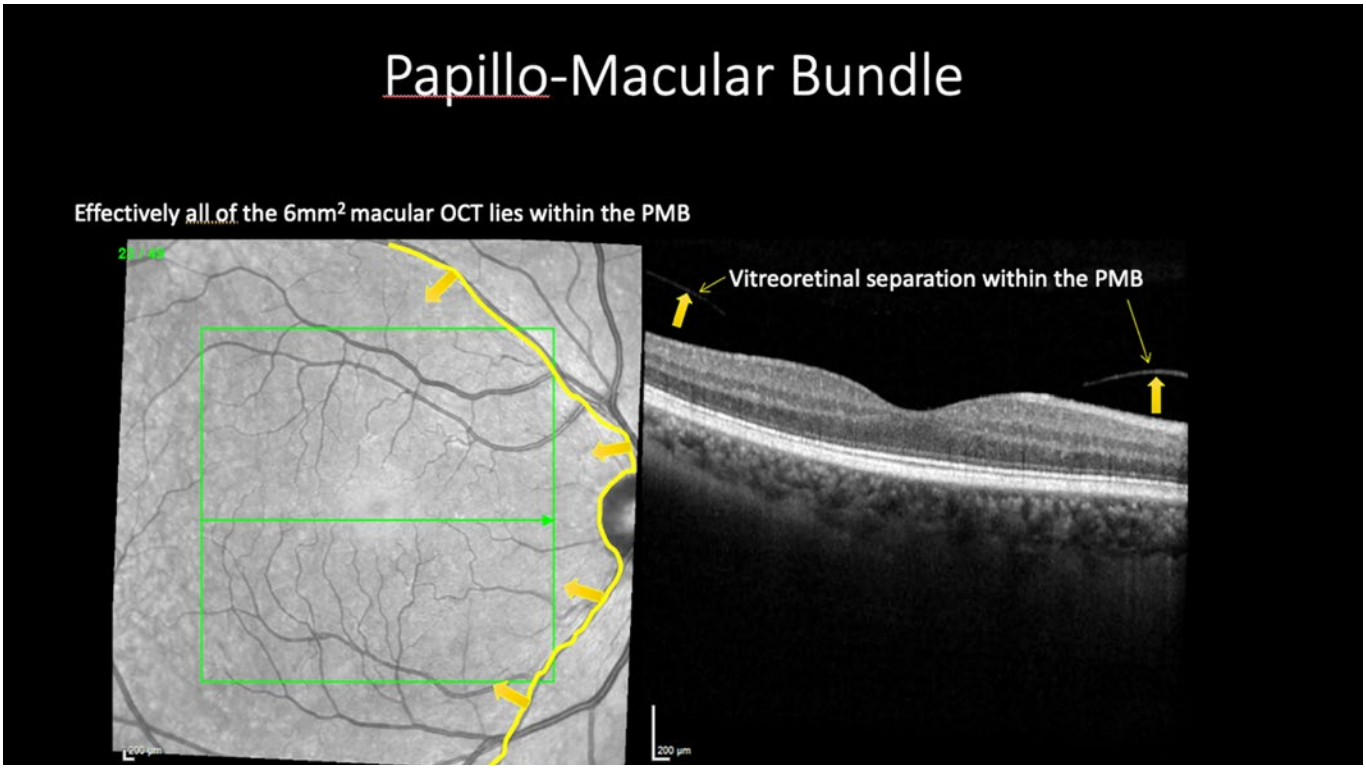


Figure 7

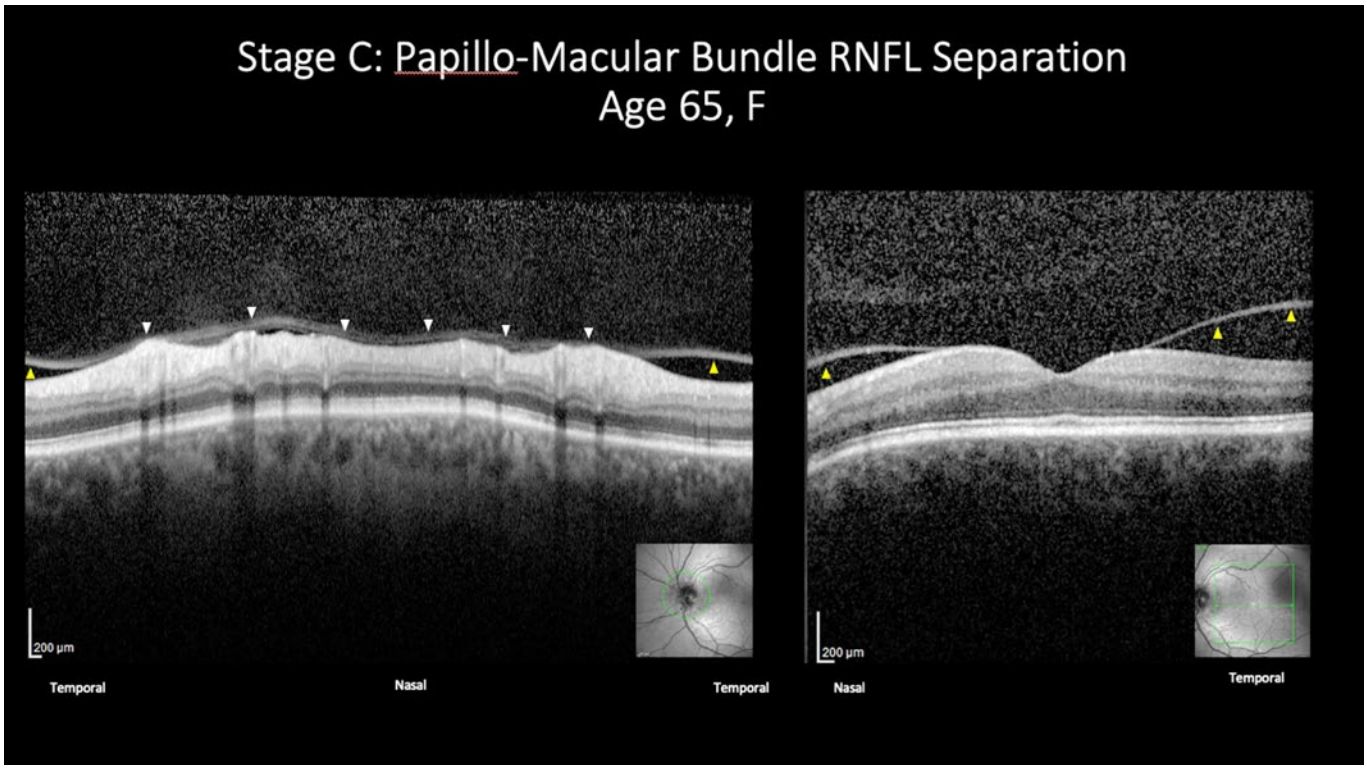


Figure 8

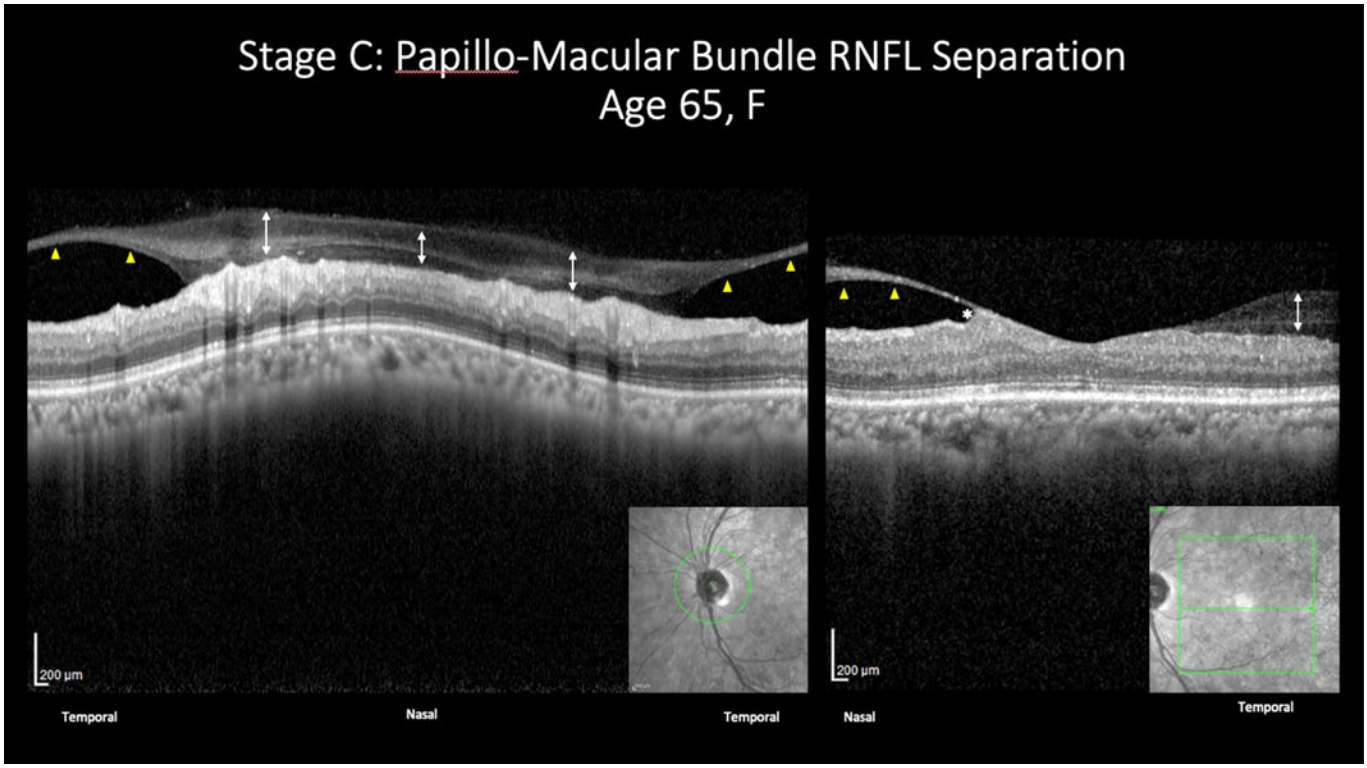


Figure 9. Stingray sign!

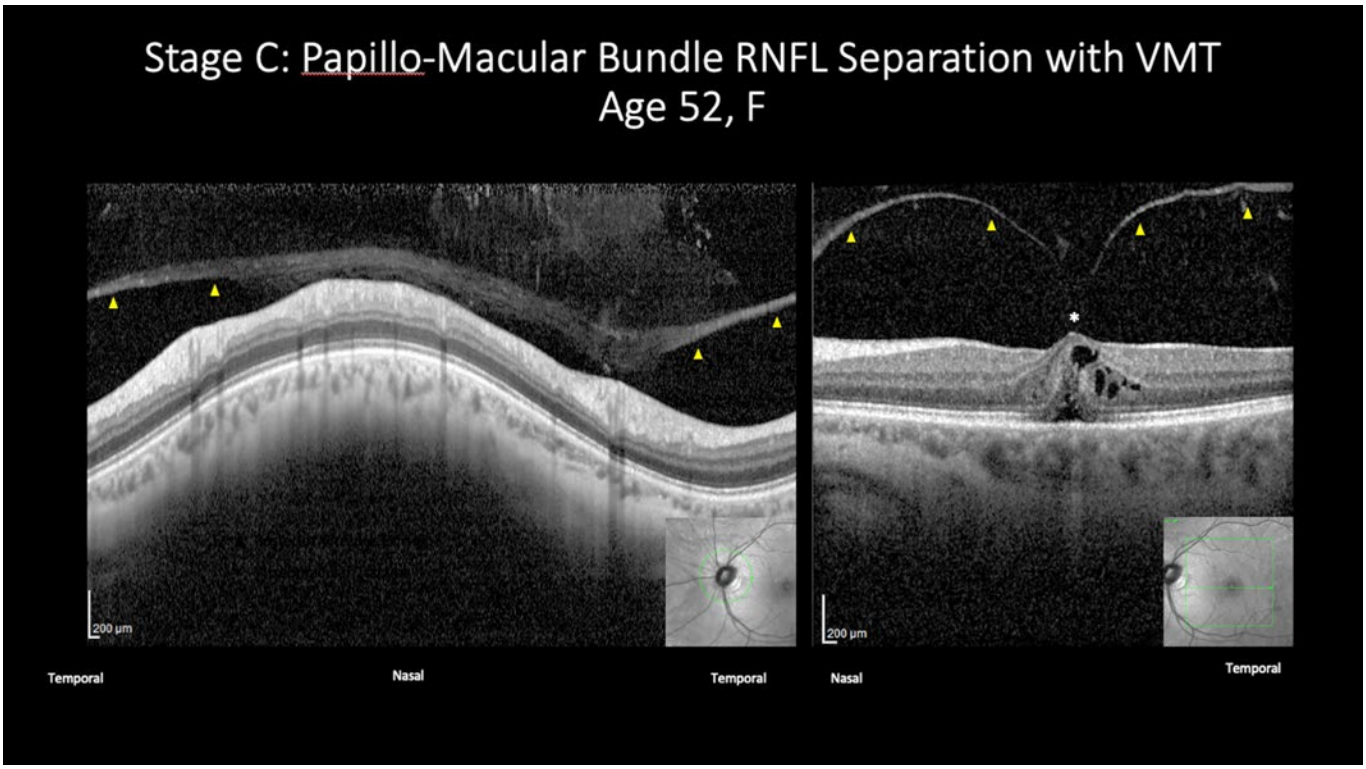


Figure 10

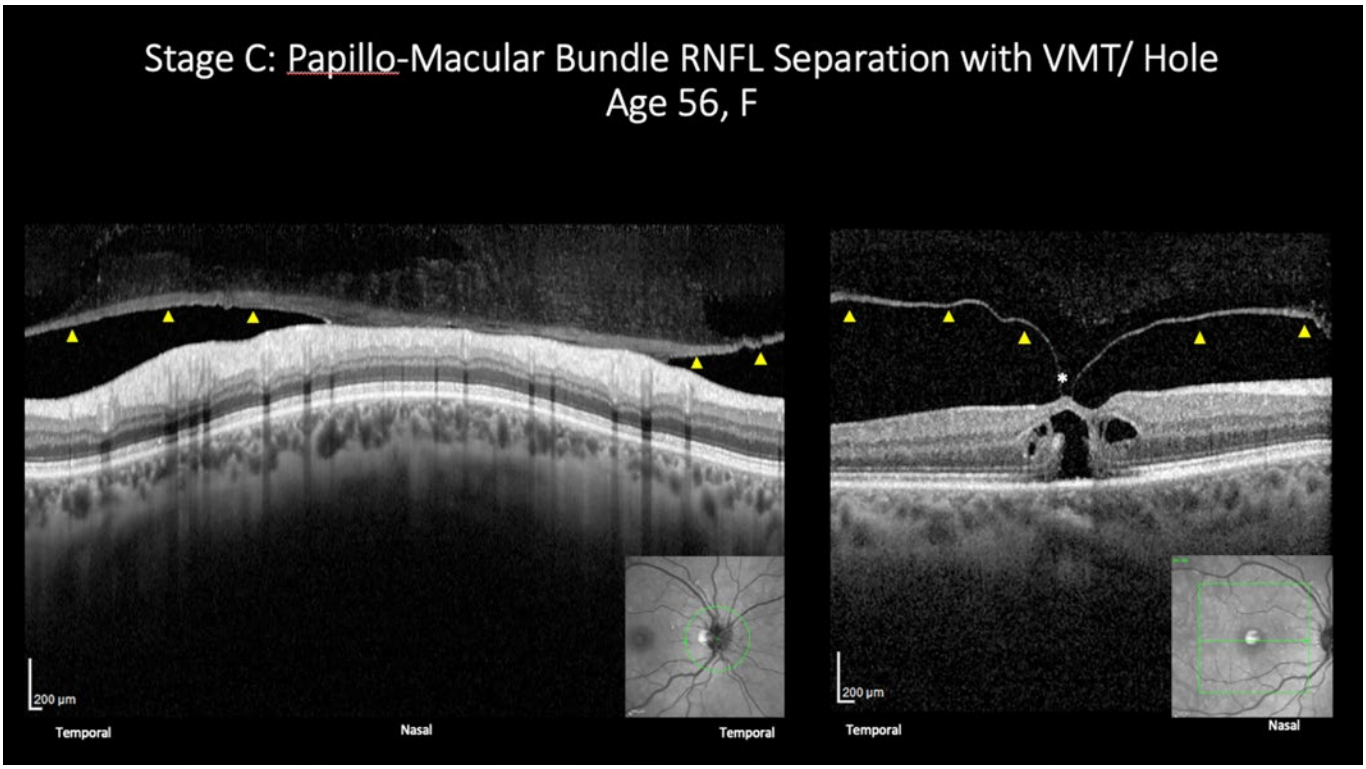


Figure 11

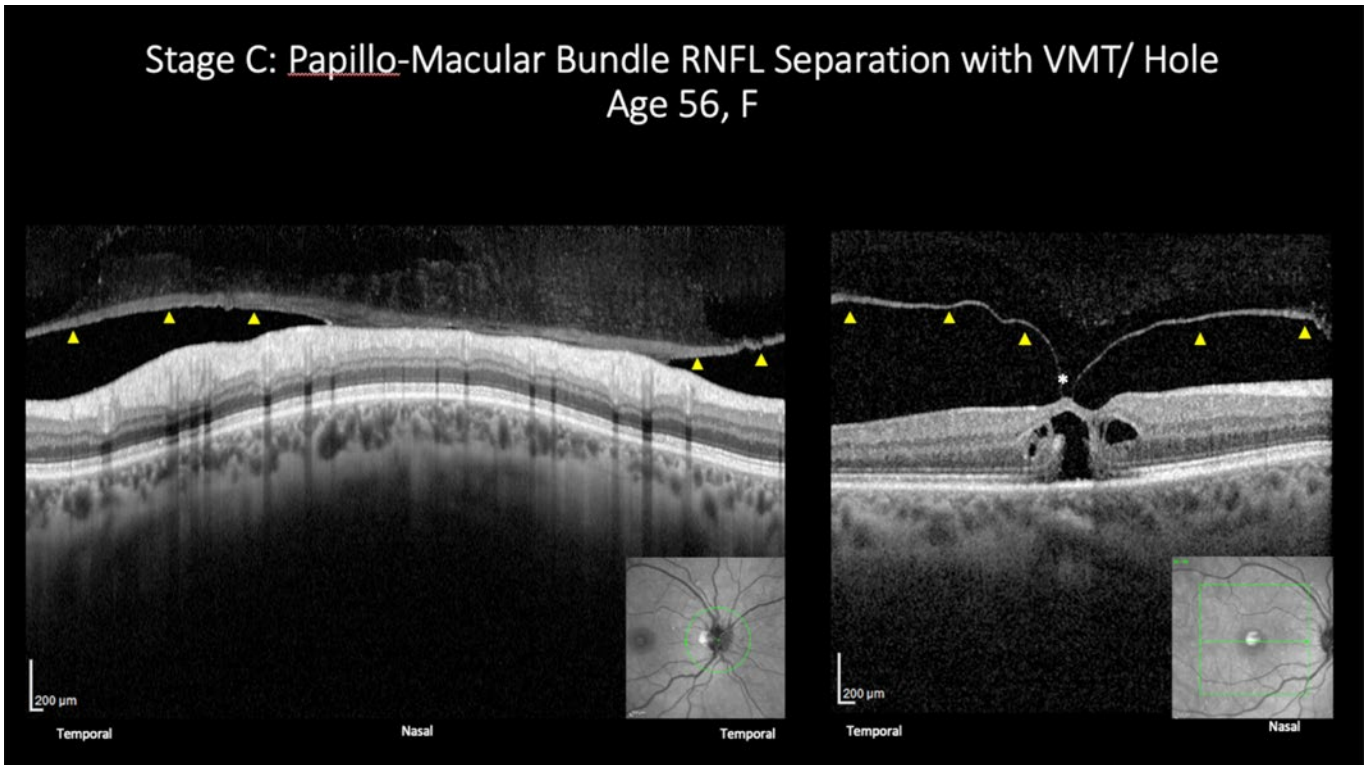


Figure 12

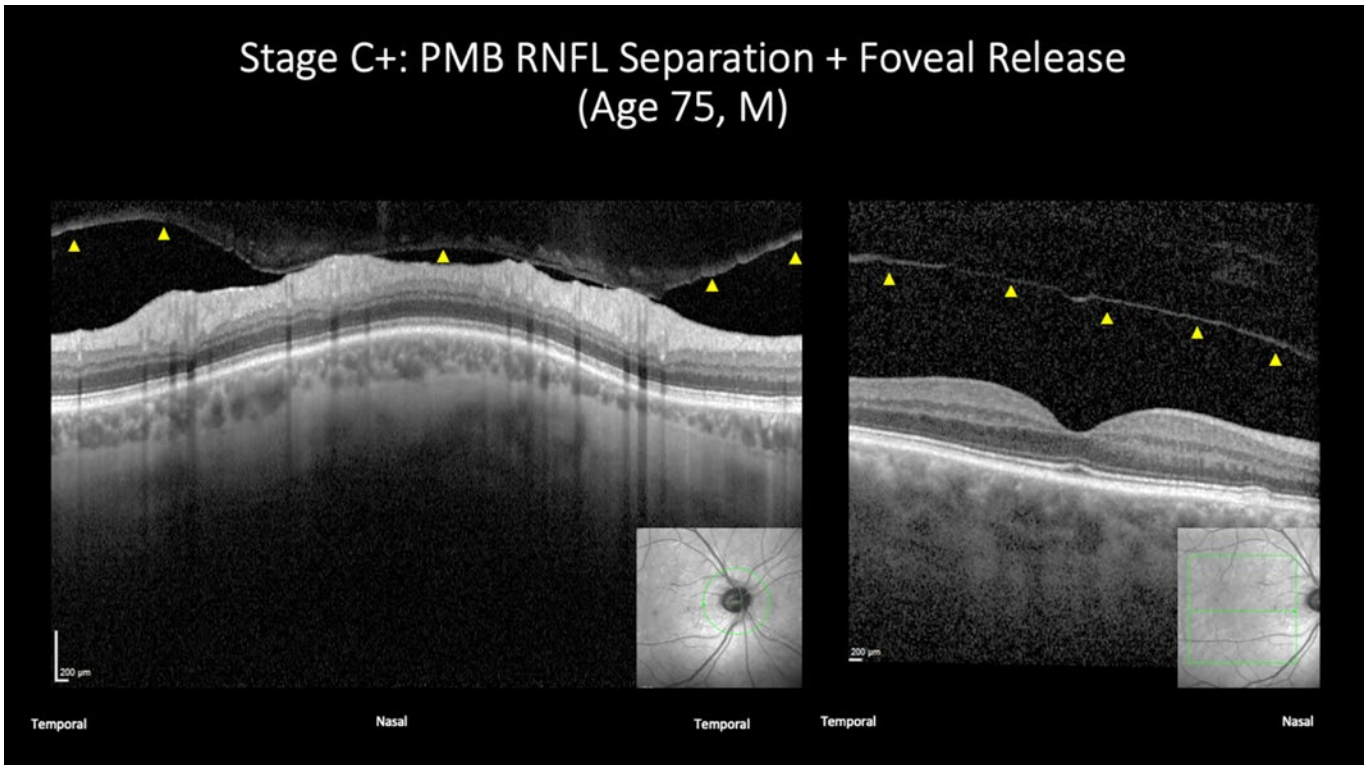


Figure 13

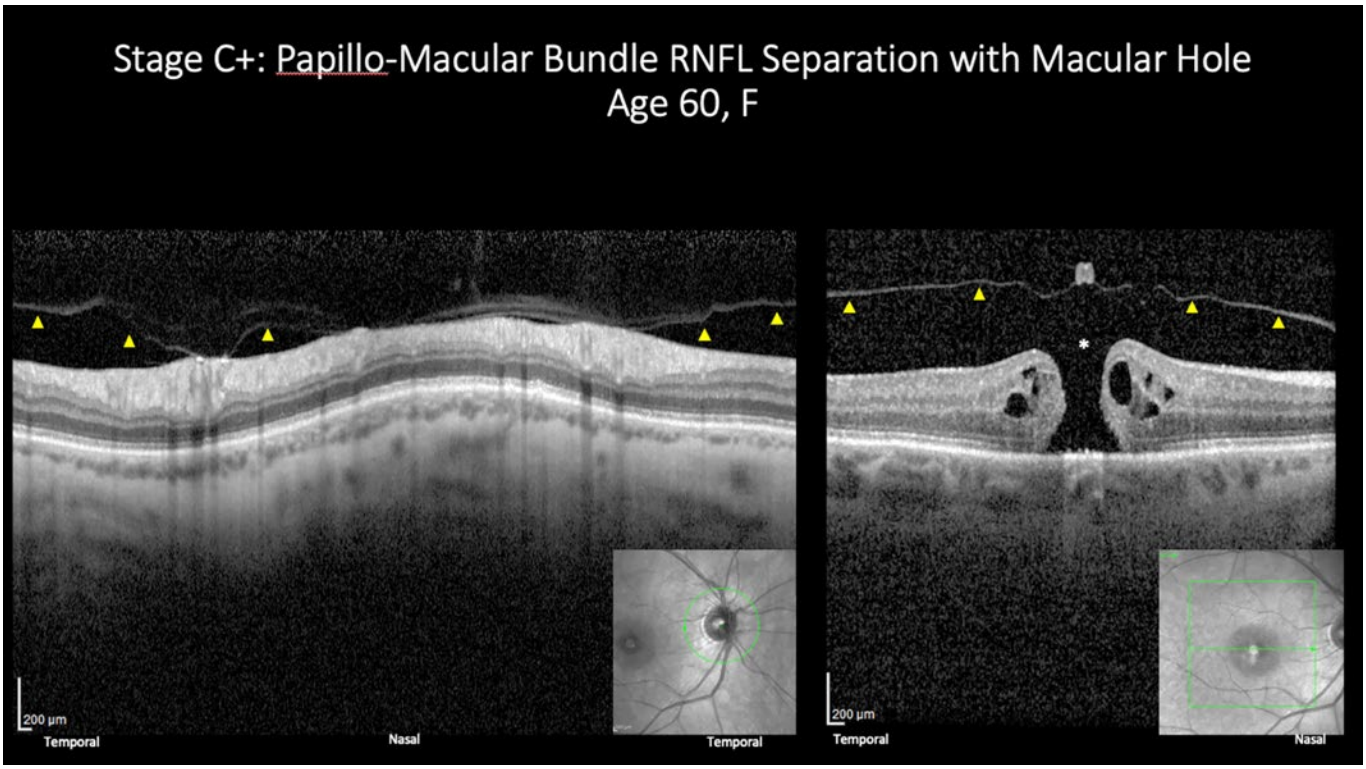


Figure 14

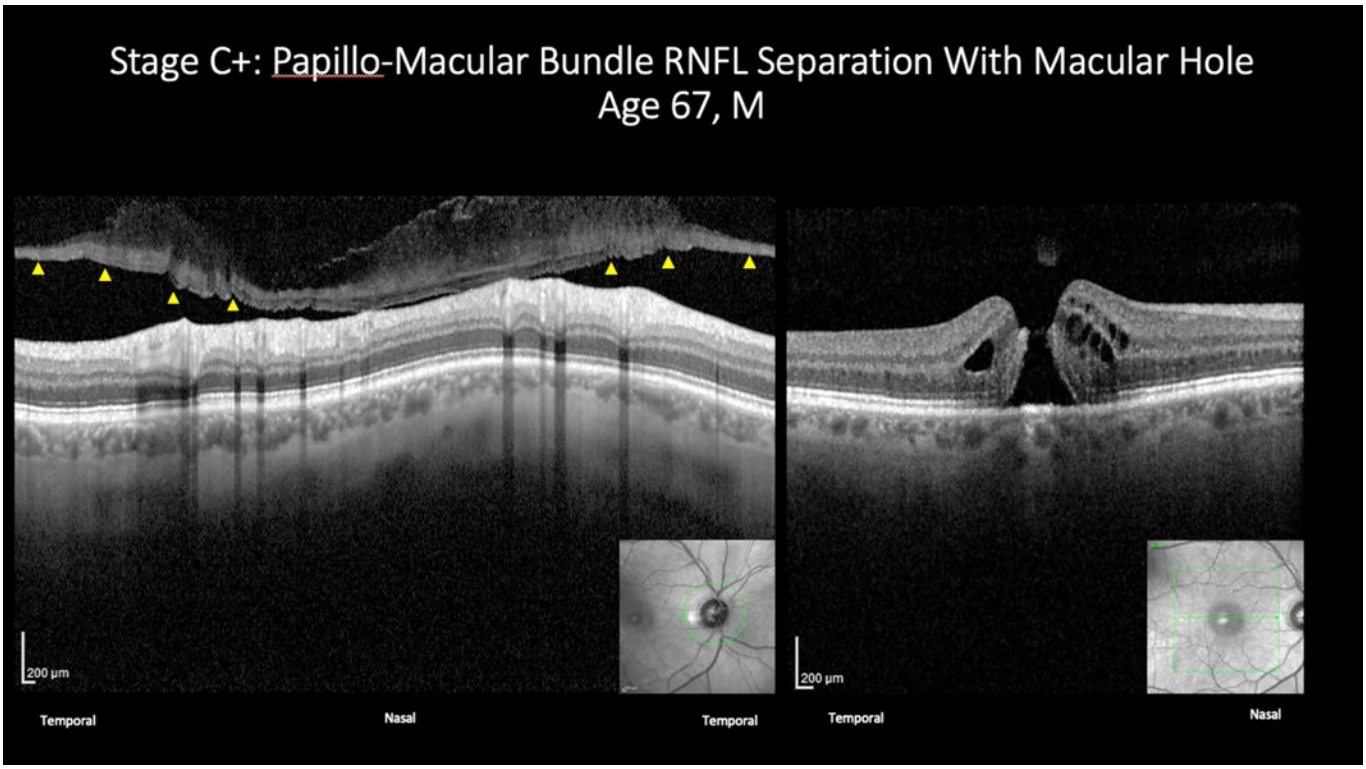


Figure 15

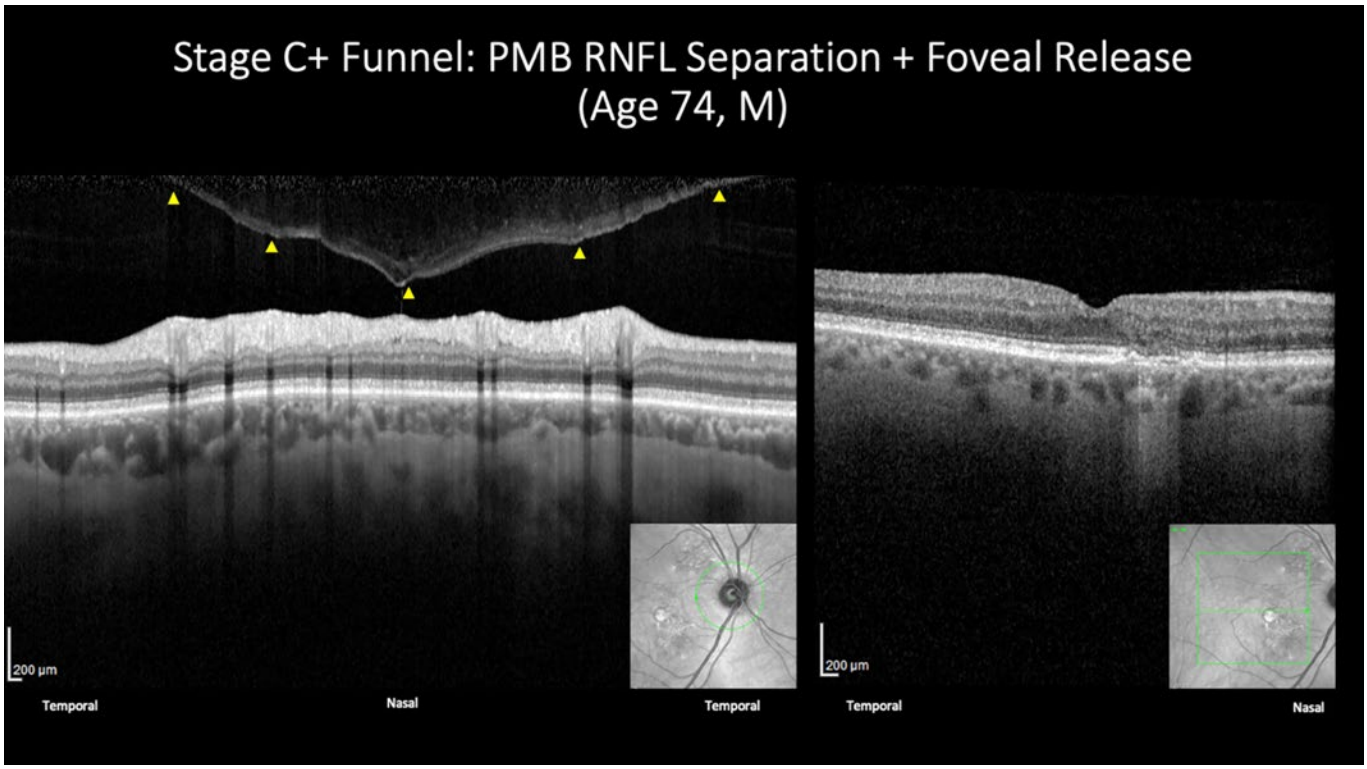


Figure 16

Stage D. Done!

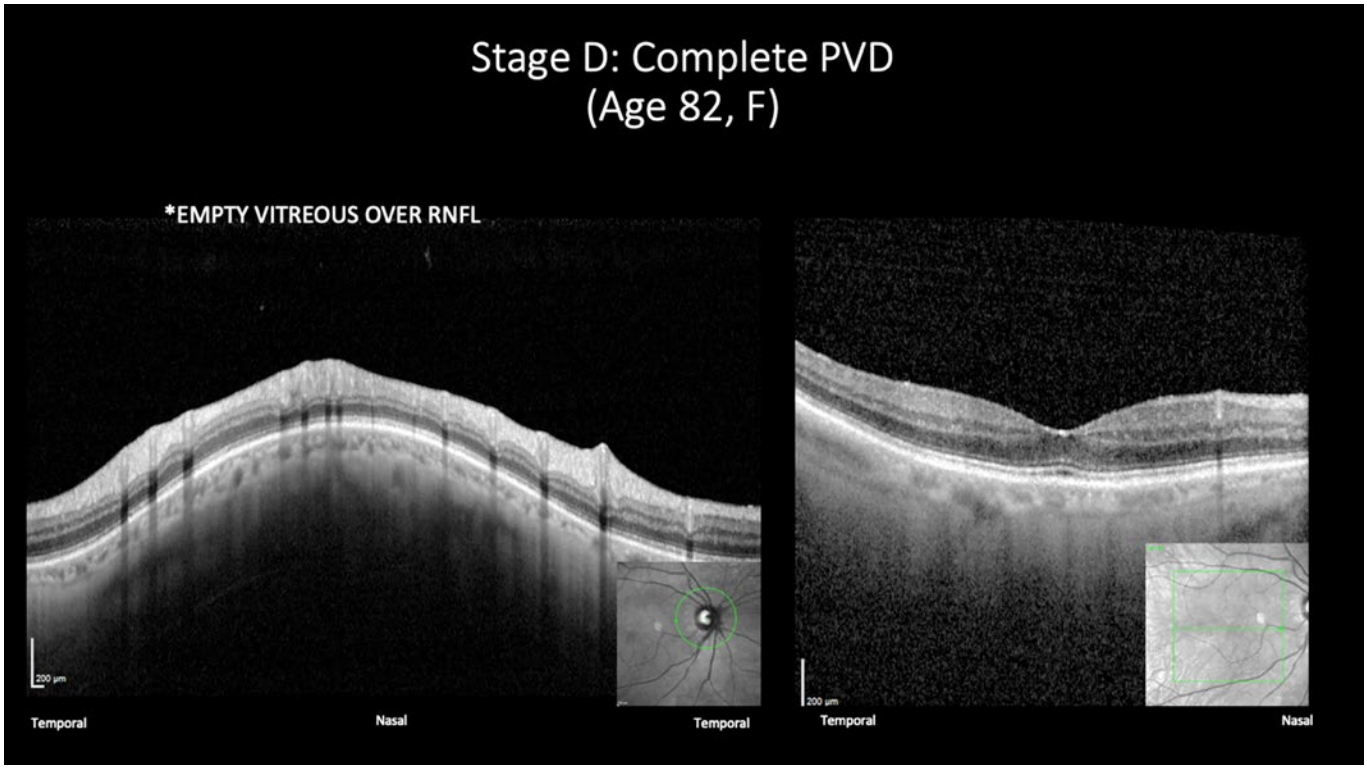


Figure 17

IV. Analysis by Age and Complications

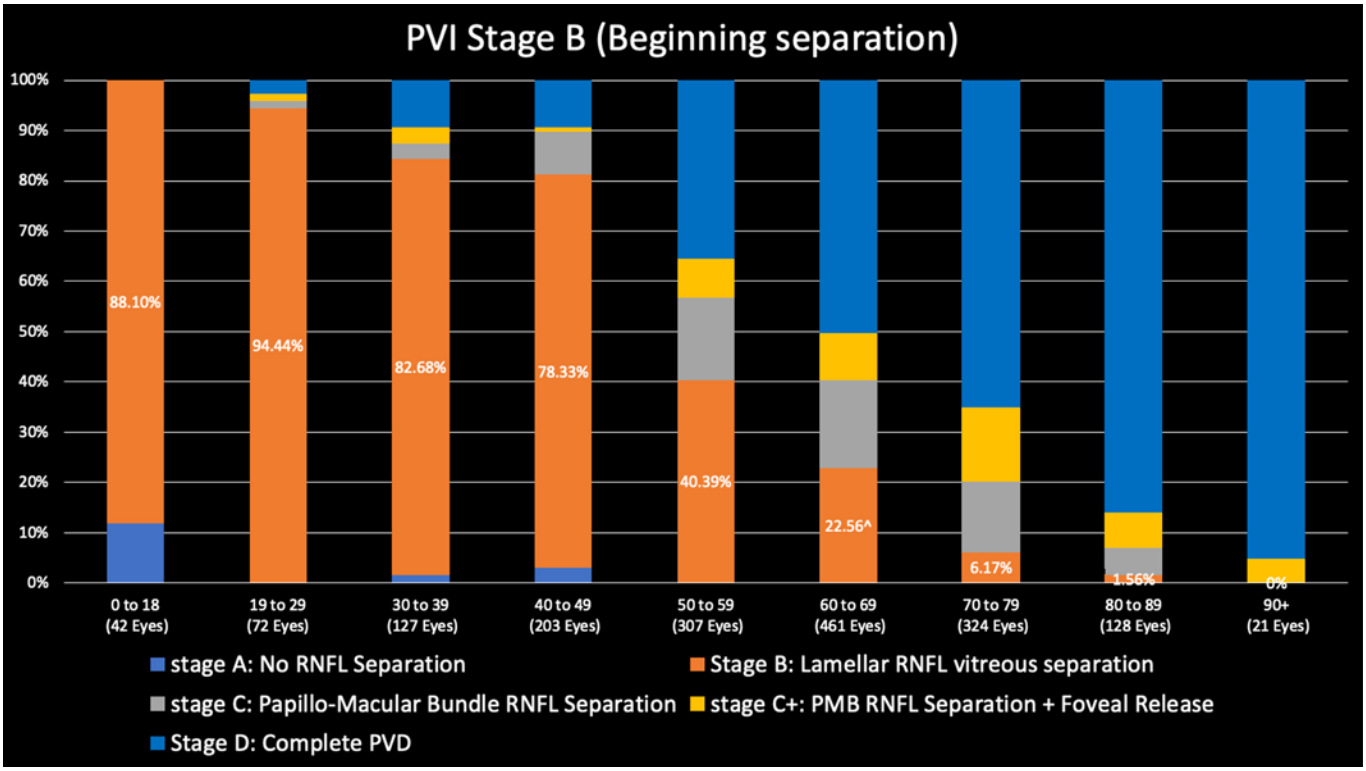


Figure 18

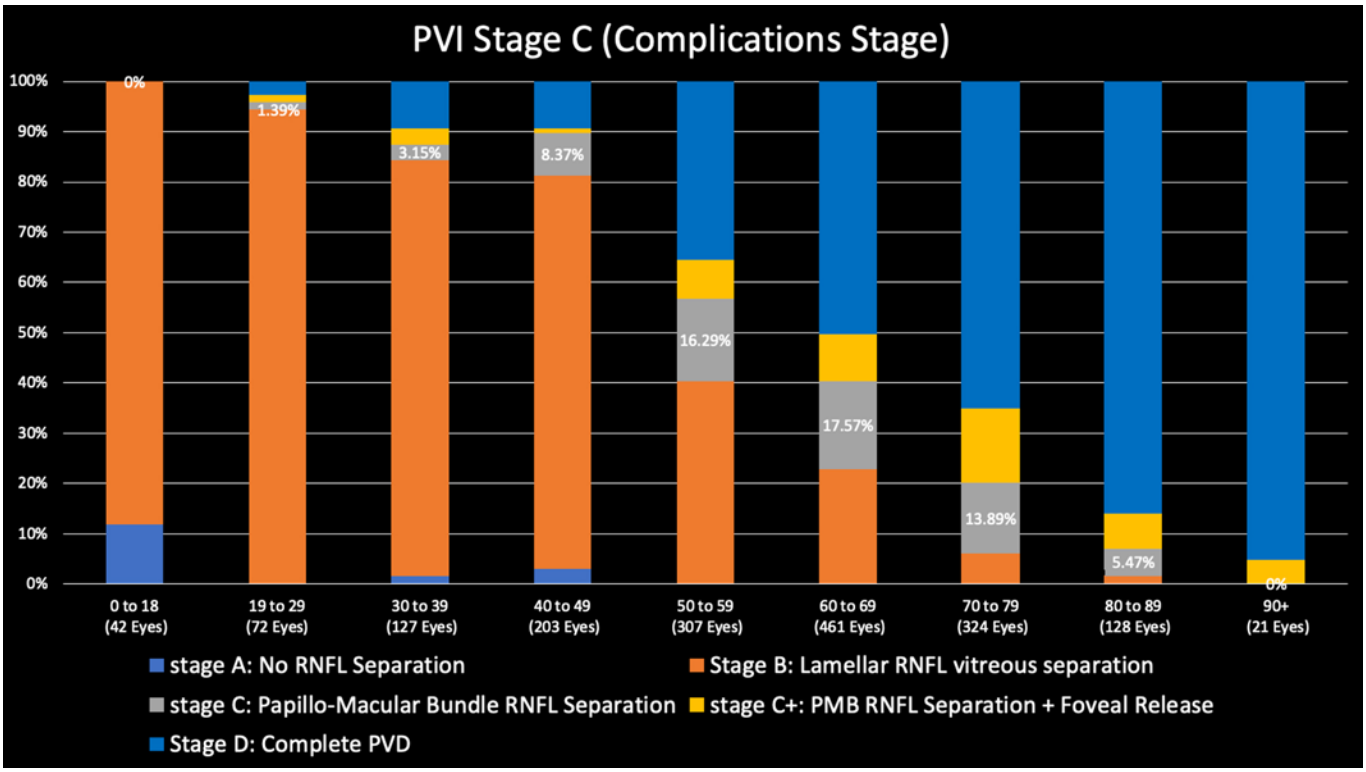


Figure 19

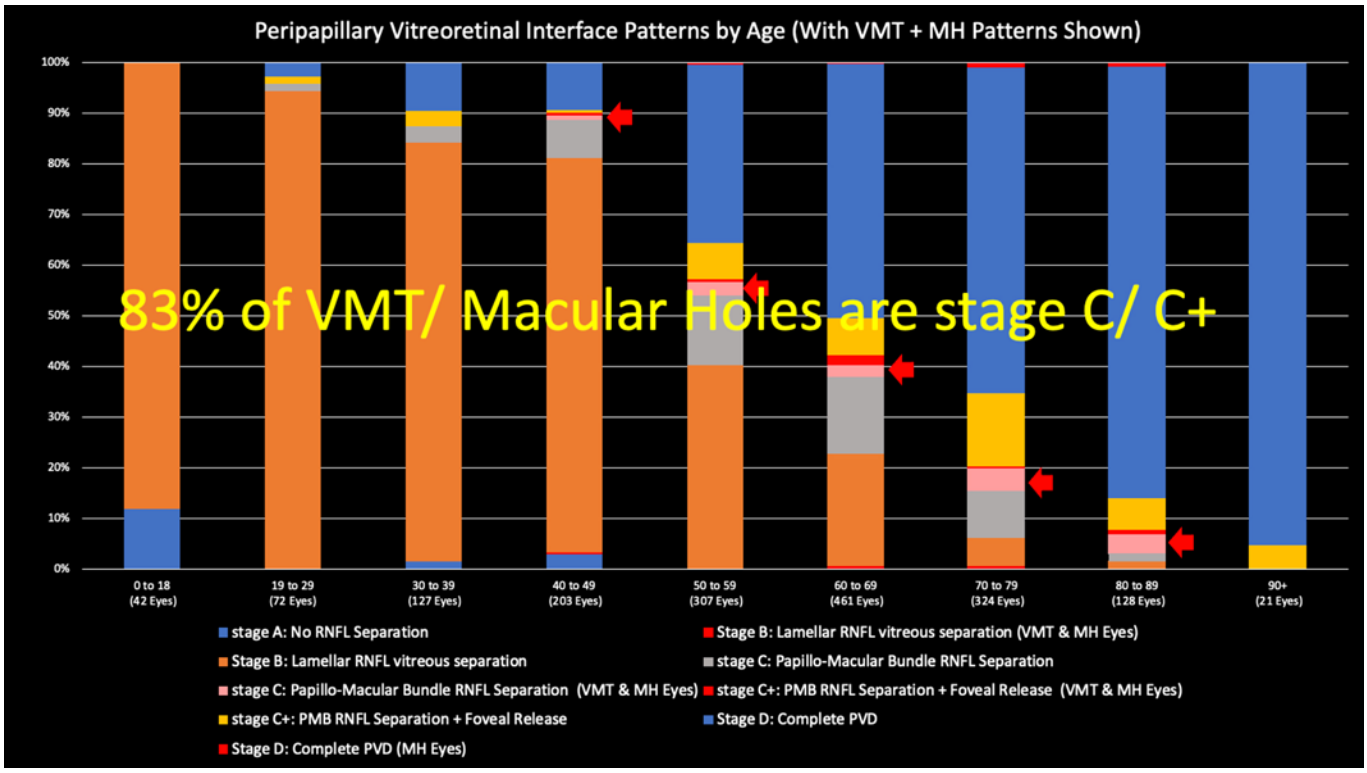


Figure 20

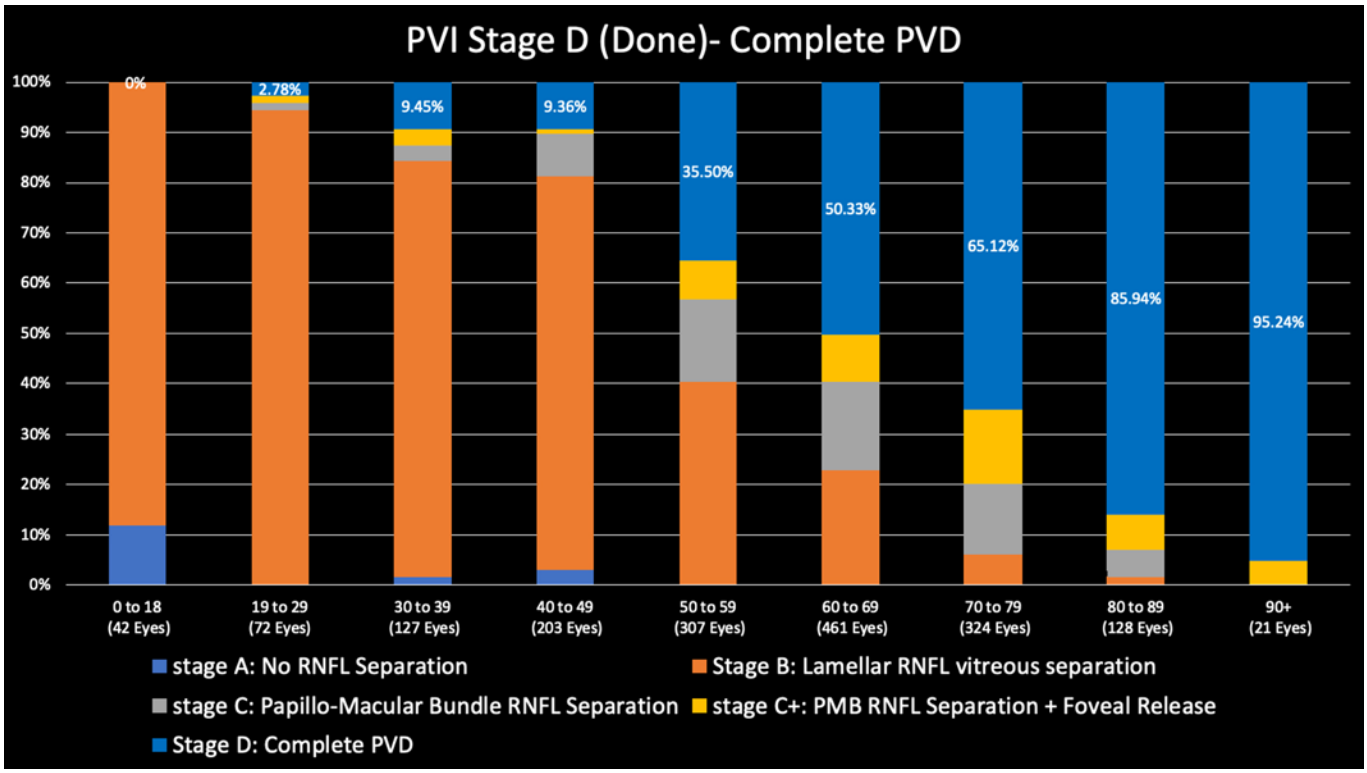


Figure 21

V. Conclusions

A. This 10-minute talk will change your life.

B. Simple existing 10-second Heidelberg RNFL scan can accurately stage PVD, allowing better diagnosis/treatment of vitreomacular pathology (macular holes, VMT) and retinal detachment surgery

C. 83% of VMT/ macular holes are stage C/C+.

D. Demonstrates that historical age ranges of PVD are too narrow. Vitreous separation begins in most eyes before the third decade, and 35% of septuagenarians do not have a total PVD.

OCT Imaging With Optical Attenuation Coefficients

Philip J Rosenfeld MD PhD, Zhongdi Chu PhD, and Ruikang K Wang PhD

Introduction

The different layers of the retina are characterized by optical properties, such as light absorption, light scattering, and light backscattering, and anisotropic factors defined by the physical nonuniformity of these layers relative to the incident light wavelength, and these properties in aggregate are responsible for image formation in conventional OCT. Optical attenuation occurs as light passes through the tissue in one direction, and then the backscattered light is attenuated once again before it reaches the instrument's detector. The overall attenuation is defined by the sum of the tissue's optical properties, which is known as the "total attenuation coefficient" or the "optical attenuation coefficient" (OAC). Vermeer et al were the first to report the use of these optical attenuation coefficients to reconstruct a depth-resolved retinal image based on OCT intensity signals.[1]

Optical attenuation coefficients are derived from the OCT datasets.

Once the OCT datasets are acquired, the OACs are calculated for each pixel using a depth-resolved single scattering model developed by Vermeer et al[1] and further refined by Zhou et al.[2,3] Figure 1 shows an example of an OCT B-scan and its corresponding OAC B-scan in which the typical retinal layers seen on OCT image (Figure 1A) are replaced by the OACs corresponding to these layers (Figure 1B). Not only is the retinal pigment epithelium (RPE) layer the brightest signal on routine OCT imaging, but it also has the largest OAC. This example also shows that the RPE is heavily attenuated where there's a choroidal hypertransmission defect (hyperTD), as seen on the typical OCT image. On the OAC B-scan, there is an obvious gap in a region with a decreased OAC value, which corresponds to the attenuated RPE and choroidal hyperTDs seen on the typical OCT B-scan. While this example is from a swept source OCT (SS-OCT) dataset, the methodology used to generate these images can be applied to spectral domain OCT (SD-OCT) datasets as well.

OAC elevation maps can depict drusen and regions evolving into geographic atrophy (GA).

By combining boundary-specific segmentation from routine OCT scans with the OAC B-scans, we've shown that it's possible to create 3-dimensional maps and en face images from the OAC signal. In Figure 2A, the OCT dataset is segmented between the retinal ganglion cell layer and the Bruch membrane (BM). This provides depth-encoded information within this slab to calculate the distance from the BM to the maximum OAC value. In Figure 2B, a slab from 64 microns to 400 microns beneath the BM is segmented, and this sub-RPE slab is ideal for providing en face images of the choroidal hyperTDs that correspond to regions with attenuated or absent RPE.

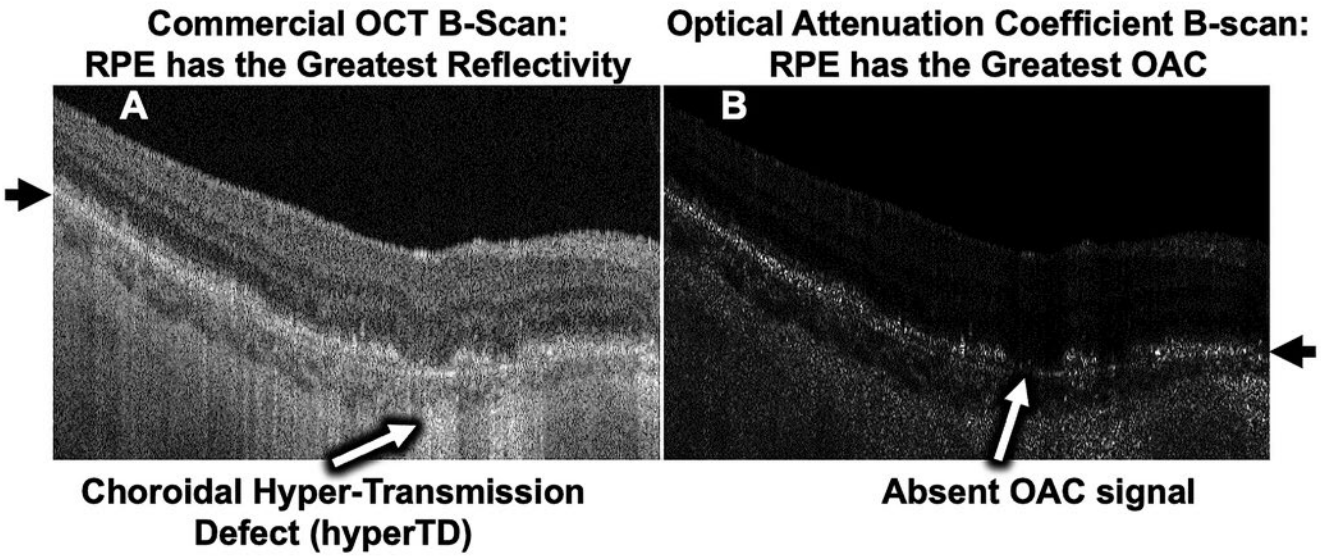


Figure 1. Example of a traditional OCT B-scan and its corresponding optical attenuation coefficient (OAC) B-scan. (A) OCT B-scan from a patient diagnosed with geographic atrophy; white arrow indicates a region with a choroidal hyper-transmission defect (hyperTD) caused by compromised retinal pigment epithelium (RPE). (B) In the corresponding OAC B-scan of panel A, the solid white arrow indicates an area where the OAC signal is diminished, which is responsible for the choroidal hyperTDs seen in the choroid in Panel A.

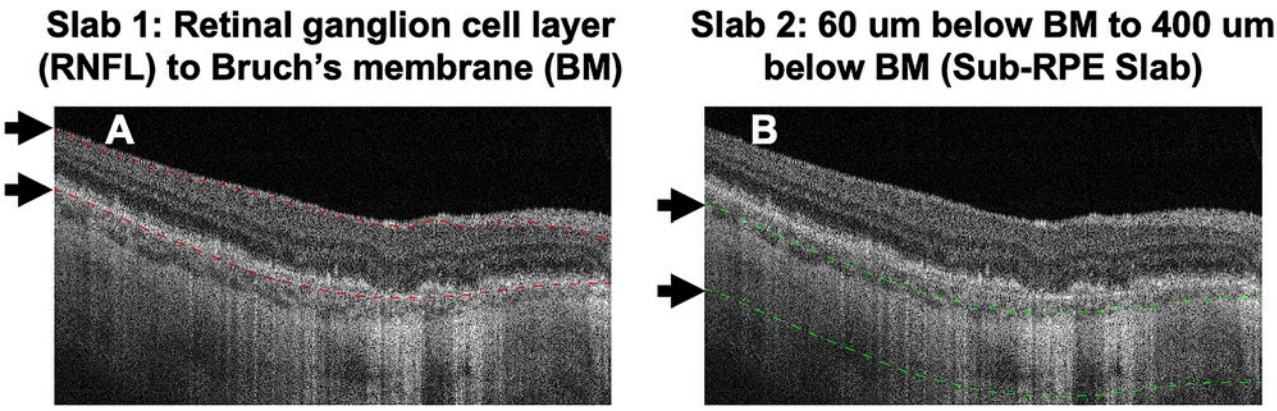


Figure 2. Images of traditional B-scans showing segmentation boundaries used to determine distances in the retina and en face images of choroidal hyper-transmission defects (hyperTDs). (A) OCT B-scan with red dashed lines and arrows corresponding to a retinal slab extending from the Bruch membrane to the ganglion cell layer. (B) OCT B-scan with green dashed lines and arrows corresponding to a retinal slab extending from 64 microns to 400 microns below the Bruch membrane, which is used for en face imaging of the choroidal hyperTDs that correspond to geographic atrophy.

Figure 3 shows 5 different images obtained from the same scan of a patient, and this scan contains drusen, drusen evolving into GA, and GA. Figure 3A shows the en face sub-RPE slab derived from the segmentation shown in Figure 2B that detects choroidal hyperTDs as areas that appear bright, which correspond to GA as well as the regions that are evolving into GA. Figures 3B-E show 4 different en face OAC images that were generated using the maximum projection image as follows: OAC max projection image between the ganglion cell layer and Bruch membrane (Fig. 3B); the sum projection image (OAC sum projection image between the ganglion cell layer and BM; Fig. 3C); the color OAC elevation map, showing the distance from BM to the maximum OAC value (Fig. 3D) where typical drusen are shown as red; and the false color OAC image, which is a composite of OAC max image (red channel), OAC sum image (green channel), and the OAC elevation map (blue channel) as shown in Fig. 3E. Figure 3A depicts drusen, and drusen with cores that have hyperTDs seen as bright spots on the sub-RPE slab and dark spots on the OAC maps (Figs 3B-E), which likely correspond to the areas of incomplete RPE and outer retinal atrophy (iRORA).[4,5] However, the regions that are dark on both the sum (Fig. 3B) and max projections (Fig. 3C) of the OAC projection maps correspond to GA, also known as complete RPE and outer retinal atrophy (cRORA).[5,6]

Future Applications of OCT Imaging With OACs

OAC imaging can be used with both SS-OCT and SD-OCT datasets to identify areas with the highest OAC, and when combined with segmentation strategies that identify BM, the OAC sum, max, and elevation maps can be generated. This strategy replaces the need to use a specific segmentation strategy to identify the RPE, which frequently fails when used to delineate large RPE elevations, such as RPE detachments,[7] as well as areas with shallow RPE elevations, such as the detection of nonexudative treatment-naïve macular neovascularization (MNV).[8] The advantage of this strategy is that any OCT features characterized by an elevated OAC can be imaged and quantified on B-scans or en face maps, and this includes hemorrhages, inflammation, exudates, and pigment.

Summary

OCT imaging with OACs allows for depth-resolved imaging of any feature that is characterized by an elevated OAC, which corresponds to an OCT feature with increased reflectivity. This OAC segmentation complements existing boundary detection algorithms and provides a strategy that can be combined with existing segmentation algorithms to provide depth encoded information. In studying the evolution of intermediate to late nonexudative and exudative AMD, the use of OCT imaging with OACs provides a unique opportunity to study disease progression from drusen, to iRORA, to cRORA, and MNV using a single OCT angiographic volume scan by applying different algorithms to identify different stages of disease progression.

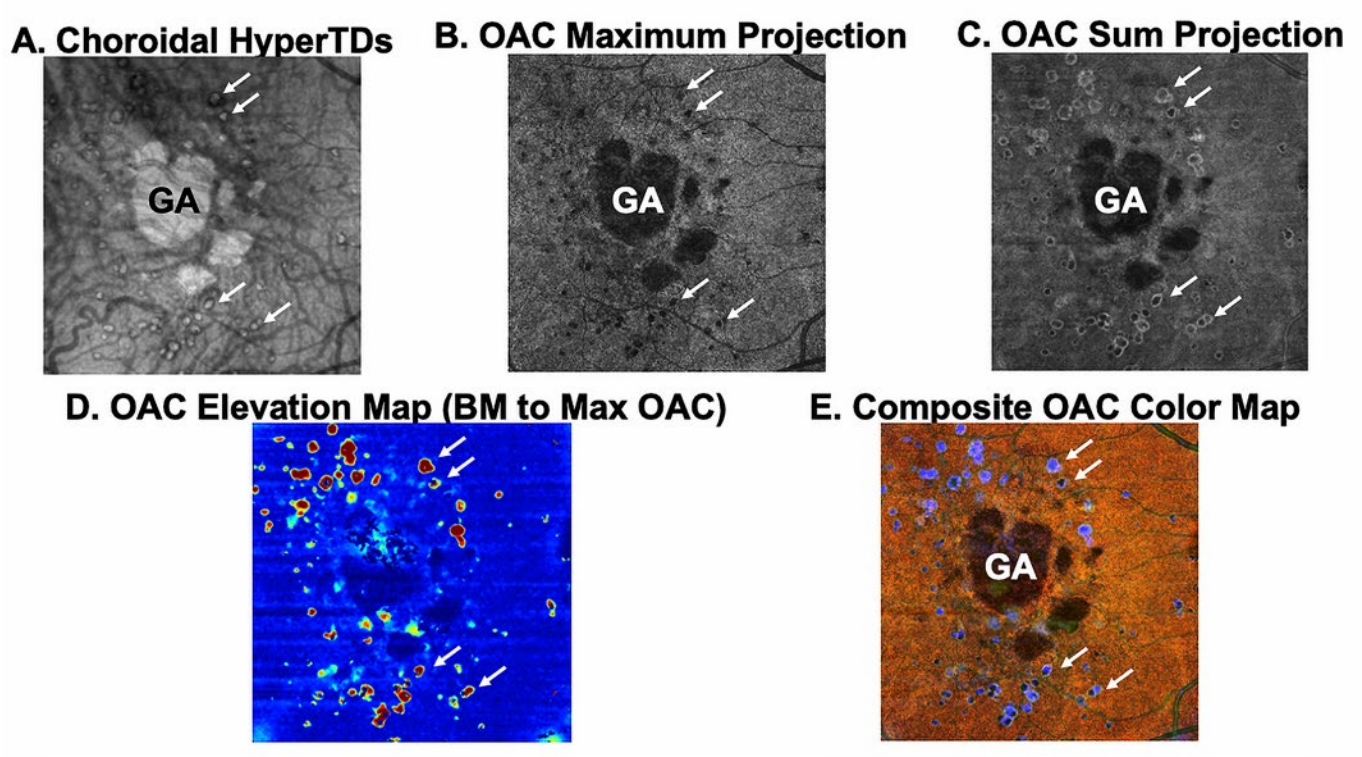


Figure 3. Images obtained using the optical attenuation coefficient (OAC) maps based on the boundary segmentation shown in Figure 2A and a traditional en face OCT image using the boundary segmentation from Figure 2B. (A) Traditional OCT en face image of the slab beneath the Bruch membrane (BM) showing the large bright choroidal hyper-transmission defect corresponding to geographic atrophy (GA) along with bright focal areas that correspond to drusen. (B) OAC maximum projection en face image of the slab depicted in Figure 2A. (C) OAC sum projection en face image of the slab in Figure 2A showing the summation of the OACs between BM and the inner retina. Those areas that look the same in panels B and C correspond to GA. Areas that appear different correspond to drusen with choroidal-hypertransmission defects. (D) Color-coded OAC elevation map with the red areas corresponding to an elevated OAC consistent with typical drusen. (E) A composite false color OAC image in which the OAC max image appears red, the OAC sum image appears green, and the OAC elevation map appears blue. In this color-coded map, the drusen appear blue and the dark regions correspond to an absent OAC signal.

References

1. Vermeer KA, Mo J, Weda JJ, et al. Depth-resolved model-based reconstruction of attenuation coefficients in optical coherence tomography. *Biomed Opt Express*. 2013; 5(1):322-337.
2. Zhou H, Chu Z, Zhang Q, et al. Attenuation correction assisted automatic segmentation for assessing choroidal thickness and vasculature with swept-source OCT. *Biomed Opt Express*. 2018; 9(12):6067-6080.
3. Zhou H, Dai Y, Shi Y, et al. Age-related changes in choroidal thickness and the volume of vessels and stroma using swept-source OCT and fully automated algorithms. *Ophthalmol Retina*. 2020; 4(2):204-215.
4. Guymer RH, Rosenfeld PJ, Curcio CA, et al. Incomplete retinal pigment epithelial and outer retinal atrophy in age-related macular degeneration: Classification of Atrophy Meeting Report 4. *Ophthalmology* 2020; 127(3):394-409.
5. Jaffe GJ, Chakravarthy U, Freund KB, et al. Imaging features associated with progression to geographic atrophy in age-related macular degeneration: Classification of Atrophy Meeting Report 5. *Ophthalmol Retina*. Epub ahead of print 2020 Dec 22. doi: 10.1016/j.oret.2020.12.009.
6. Sadda SR, Guymer R, Holz FG, et al. Consensus definition for atrophy associated with age-related macular degeneration on OCT: Classification of Atrophy Meeting Report 3. *Ophthalmology* 2018; 125(4):537-548.
7. Kim K, Yang J, Feuer W, et al. A comparison study of polypoidal choroidal vasculopathy imaged with indocyanine green angiography and swept-source optical coherence tomography angiography. *Am J Ophthalmol*. 2020; 217:240-251.
8. Shen M, Zhang Q, Yang J, et al. Swept-source OCT angiographic characteristics of treatment-naive nonexudative macular neovascularization in AMD prior to exudation. *Invest Ophthalmol Vis Sci*. 2021; 62(6):14.

OCT Angiography Update

Nadia K Waheed MD

OCT angiography (OCT-A) enables us to visualize the retinal and choroidal microvasculature in a noninvasive manner. Generating quantifiable maps of the retinal microvasculature, OCT-A is fast, depth resolved, and easily deployed in current-generation OCT devices. For these reasons, it has become an important tool in clinical practice as well as in clinical trials looking at the retinal vasculature. This presentation will focus on the following topics:

I. Overview of OCT-A Principles

II. Technological Considerations in OCT-A

- A. Swept source allowing for acquisition of larger fields of view in comparable acquisition times
- B. Widefield OCT-A for the assessment of diabetic retinopathy, retinal vascular occlusions, and vasculitis/uveitis

III. OCT-A Metrics

- A. Measuring relative blood flow speeds: variable interscan time analysis OCT angiography (VISTA)
- B. Repeatability and reproducibility of OCT-A metrics and how these metrics correlate with stages and progression of retinal diseases
- C. Retinal microvasculature and its association with systemic diseases
  1. Cerebrovascular disease (Alzheimer, stroke, small vessel disease)
  2. Neuroinflammatory diseases (multiple sclerosis)
  3. Cardiovascular diseases

IV. Artificial Intelligence and OCT-A

- A. Averaging and denoising algorithms
- B. Disease detection and classification

V. Correlations Between Structure and Function: OCT-A and Microperimetry for Retinal Diseases

Imaging Panel Discussion: OCT Diagnoses You Don't Want to Miss

Panel Moderator: Jay S Duker MD

Panelists: Barbara Ann Blodi MD, Justis P Ehlers MD, Eleonora G Lad MD PhD and Nadia Khalida Waheed MD

NOTES

Late Breaking Developments, Part II

Moderator: Anat Loewenstein MD

Panelists: Colin A McCannel MD, Srinivas R Sadda MD, and Paul Sternberg Jr MD

NOTES

Unanswered Questions in AMD: Trials We Didn't Do in the DRCR Retina Network

Daniel F Martin MD

NOTES

Port Delivery System Long-term Follow-up

Interim Analysis Results of the Phase 3 Portal Trial Evaluating the Long-term Safety and Efficacy of the Port Delivery System With Ranibizumab (PDS) for Patients With Neovascular AMD

Peter A Campochiaro MD

Background

Neovascular AMD (nAMD) remains a leading cause of vision loss despite widespread use of efficacious intravitreal anti-VEGF treatments.[1-3] Optimal long-term use of anti-VEGF monotherapy is associated with high burden for patients, their caregivers, and health-care providers[4] and requires frequent injections and patient monitoring visits.[1,3,5-7] The Port Delivery System with ranibizumab (PDS) is an innovative, investigational drug delivery system with the potential to reduce treatment burden in patients with nAMD. The PDS includes a surgically placed implant for continuous delivery of a customized formulation of ranibizumab into the vitreous that is refilled via clinic-based refill-exchange procedures. The PDS clinical trial program in nAMD, including the Phase 2 Ladder (NCT02510794)[8,9] and Phase 3 Archway (NCT03677934)[10,11] trials, demonstrated that treatment with the PDS 100 mg/mL was well tolerated in most patients, with manageable complications, and resulted in vision and anatomic outcomes that were comparable with monthly intravitreal ranibizumab 0.5-mg injections (herein reported as "monthly ranibizumab"). The long-term safety and efficacy of the PDS 100 mg/mL with fixed refill-exchanges every 24 weeks (PDS Q24W) for nAMD is being evaluated in the Portal extension trial (NCT03683251).[12] The current analyses present interim long-term, pooled safety follow-up data for patients treated with PDS 100 mg/mL and efficacy data from Ladder, Archway, and Portal.

Methods

Ladder and Archway trial designs and results have been previously reported.[8-10] In Ladder, patients were randomized 3:3:3:2 to treatment with the PDS 10 mg/mL, PDS 40 mg/mL, and PDS 100 mg/mL, with pro re nata (PRN) refills administered based on protocol-defined criteria, or monthly ranibizumab. In Archway, patients were randomized 3:2 to treatment PDS Q24W or monthly ranibizumab (every 4 weeks). Portal is an ongoing, multicenter, open-label, extension study enrolling patients who completed either Ladder or Archway. In Portal, patients treated with PDS with PRN refill-exchanges in Ladder or with PDS Q24W refill-exchanges in Archway receive PDS refill-exchanges Q24W starting on study Day 1, and patients who had received monthly ranibizumab undergo PDS implantation and initial fill with ranibizumab 100 mg/mL at Day 1 of Portal and then receive PDS refill-exchanges Q24W.[12]

Herein, we report safety and efficacy results of the Portal interim data from the September 11, 2020, clinical cut-off. The long-term safety of PDS is presented by pooling patients treated with PDS 100 mg/mL in Ladder, Archway, and Portal (including those previously treated with PDS 10 mg/mL or 40 mg/mL, or with intravitreal ranibizumab, once they received PDS 100 mg/mL, herein called "pooled PDS 100 mg/mL safety population"). Cumulative rate of ocular adverse events of special interest (AESIs), including cataract, vitreous hemorrhage, conjunctival bleb/conjunctival bleb filtering leak, conjunctival erosion, implant dislocation, rhegmatogenous retinal detachment, and endophthalmitis, are reported. Efficacy data are reported separately for patients treated with PDS 100 mg/mL PRN or monthly ranibizumab in Ladder who enrolled in Portal and switched to PDS 100 mg/mL Q24W (herein called "Ladder-to-Portal patients") and for Archway patients because there were differences in refill-exchange frequency and in the number of prerandomization intravitreal anti-VEGF injections across trials. Efficacy endpoints reported include change from Ladder and Archway baseline in BCVA score, change from Ladder and Archway baseline in center point thickness (CPT), and proportion of patients from Ladder who switched to PDS Q24W in Portal and were assessed for and received supplemental treatment with intravitreal ranibizumab 0.5 mg before scheduled refill-exchanges.

Results

The pooled PDS 100 mg/mL safety population included 443 patients: Ladder-to-Portal PDS 10/40 mg/mL PRN to PDS 100 mg/mL Q24W (n = 96), Ladder PDS 100 mg/mL PRN to PDS 100 mg/mL Q24W (n = 65), Ladder or Archway monthly ranibizumab to PDS 100 mg/mL Q24W (n = 34), and Archway PDS 100 mg/mL Q24W (n = 248). The median age was 75.2 years (range: 51 to 96 years), and the average follow-up was 1.77 years (range: <1 week to 4.3 years), with 47 patients (11%) receiving at least 3 years of treatment. The retention rate was 95.9%, and there was a low impact of COVID-19 on the collection of safety data.

From Ladder or Archway baseline up to the September 2020 data cut-off, during a maximum follow-up of approximately 4 years, 148 ocular AESIs were reported, with 98 patients (22.1%) experiencing at least one ocular AESI in the study eye. The most common ocular AESIs were cataract (45 [10.2%]), the majority of which were reported as worsening or progression of cataracts and were mild or moderate in severity; vitreous hemorrhage (23 [5.2%]), the majority of which were Grade 1 or Grade 2 in severity and resolved spontaneously; conjunctival bleb/conjunctival filtering bleb leak (21 [4.7%]), the majority of which were mild or moderate; conjunctival erosion (16 [3.6%]), the majority of which were mild or moderate; implant dislocation (4 [0.9%]); and rhegmatogenous retinal detachment (3 [0.7%]). Endophthalmitis occurred in 7 patients (1.6%; 4 patients in Archway and 3 patients in Ladder), most often in conjunction with conjunctival events (3 patients with conjunctival retractions, 2 patients with conjunctival erosion).

For Ladder-to-Portal patients, after surgical recovery the mean BCVA remained relatively stable compared to Ladder

baseline through Month 36 in both the Ladder PDS 100 mg/mL PRN arm (*n* = 59) and the monthly ranibizumab arm (*n* = 41). Similarly, mean CPT from Ladder baseline remained stable through Month 36 in patients in the Ladder PDS 100 mg/mL PRN arm and remained stable with a trend toward improvement through Month 36 in the Ladder monthly ranibizumab arm.

Patients enrolled in Archway were previously treated and responsive to anti-VEGF injections. Before the first study treatment (considered as "baseline") in Archway, patients had gained an average of 11.3 BCVA ETDRS letters after a mean (SD) of 4.9 (1.3) anti-VEGF injections and 5.2 (1.9) months since diagnosis. After surgical recovery, the mean BCVA was stable compared to baseline through Week 76 in both the PDS Q24W arm (*n* = 248) and the monthly ranibizumab arm (*n* = 167), and CPT was stable in both treatment arms through Week 76 (follow-up after Week 60 is incomplete).

In Portal, for Ladder patients who switched from PDS 100 mg/mL PRN or monthly ranibizumab to PDS Q24W, the rate of supplemental treatment with intravitreal ranibizumab 0.5 mg was 0% during the first treatment interval, 5.7% (3/53) for the Ladder PDS 100 mg/mL arm and 3.6% (1/28) for the Ladder monthly ranibizumab arm during the second interval, and 0% during the third interval.

Discussion

The long-term safety profile of the PDS 100 mg/mL, with a subset of patients with more than 3 years of follow-up, reveals no new safety signals. Overall, complications have been manageable, with 1 of 443 patients (0.23%) experiencing severe irreversible loss of vision. The PDS surgical procedures have evolved based on learnings from the clinical trial program since Ladder to support optimal patient outcomes. Long-term efficacy outcomes with PDS 100 mg/mL demonstrate stable BCVA and CPT from Ladder baseline to Portal data cut-off (36 months from implantation), as well as from Archway baseline to 76 weeks (19 months from implantation). These long-term data suggest that the PDS 100 mg/mL reliably controls nAMD in the long term, with a very low rate of severe, irreversible vision loss due to complications. Additional follow-up in Portal for patients previously enrolled in Ladder or Archway is ongoing.

References

1. Flaxel CJ, Adelman RA, Bailey ST, et al. Age-related macular degeneration Preferred Practice Pattern®. *Ophthalmology* 2020; 127(1):P1-P65.
2. Flaxman SR, Bourne RRA, Resnikoff S, et al. Global causes of blindness and distance vision impairment 1990-2020: a systematic review and meta-analysis. *Lancet Glob Health*. 2017; 5(12):e1221-e1234.
3. Wykoff CC, Clark WL, Nielsen JS, Brill JV, Greene LS, Heggen CL. Optimizing anti-VEGF treatment outcomes for patients with neovascular age-related macular degeneration. *J Manag Care Spec Pharm*. 2018; 24(2-a suppl):S3-S15.
4. Prenner JL, Halperin LS, Rycroft C, Hogue S, Williams Liu Z, Seibert R. Disease burden in the treatment of age-related macular degeneration: findings from a time-and-motion study. *Am J Ophthalmol*. 2015; 160(4):725-731.e1.
5. Eylea [package insert]. Tarrytown, NY: Regeneron Pharmaceuticals, Inc.; 2019.
6. Lucentis [package insert]. South San Francisco, CA: Genentech, Inc.; 2018.
7. Maguire MG, Martin DF, Ying GS, et al; Comparison of Age-related Macular Degeneration Treatments Trials (CATT) Research Group. Five-year outcomes with anti-vascular endothelial growth factor treatment of neovascular age-related macular degeneration: the comparison of age-related macular degeneration treatments trials. *Ophthalmology* 2016; 123(8):1751-1761.
8. Campochiaro PA, Marcus DM, Awh CC, et al. The Port Delivery System with ranibizumab for neovascular age-related macular degeneration: results from the randomized Phase 2 Ladder clinical trial. *Ophthalmology* 2019; 126(8):1141-1154.
9. Khanani AM, Callanan D, Dreyer R, et al. End-of-study results for the Ladder Phase 2 trial of the Port Delivery System with ranibizumab for neovascular age-related macular degeneration. *Ophthalmol Retina*. 2020; S2468-6530(20)30447-4.
10. Campochiaro PA, Singh N, Kardatzke D, et al. Primary analysis results of the Phase 3 Archway trial of the Port Delivery System with ranibizumab for patients with neovascular AMD. Oral presentation presented at 38th Annual Scientific Meeting of the American Society of Retina Specialists; July 24, 2020 (virtual meeting).
11. A Phase III study to evaluate the Port Delivery System with Ranibizumab compared with monthly ranibizumab injections in participants with wet age-related macular degeneration (Archway). ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/NCT03677934.
12. Extension study for the Port Delivery System with ranibuzumab (Portal). ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/NCT03683251.

Faricimab in Neovascular AMD: One-Year Efficacy, Safety, and Durability in the Phase 3 TENAYA and LUCERNE Trials

Carl D Regillo MD FACS

Background

Optimal vision outcomes with anti-VEGF treatment for neovascular AMD (nAMD) require frequent injections and close monitoring.[1] Real-world data suggest that this overall treatment burden creates a barrier to effective anti-VEGF treatment that contributes to many patients not achieving or maintaining vision outcomes seen in clinical trials.[2-4] The multifactorial pathophysiology of nAMD, involving other angiogenic factors besides VEGF-A as well as inflammatory pathways, suggests that treatment of nAMD could benefit from a multitargeted approach beyond anti-VEGF treatment.[5] In retinal and choroidal vascular diseases such as nAMD, angiopoietin-2 (Ang-2) and VEGF-A are upregulated and synergistically drive vascular destabilization, characterized by vascular leakage, neovascularization, and inflammation.[6-8] Therefore, dual inhibition of Ang-2 and VEGF-A may promote vascular stability, resulting in increased durability and improved long-term outcomes beyond anti-VEGF treatment alone for nAMD.

Data from the Phase 2 STAIRWAY trial (NCT03038880) suggest that dual inhibition of the angiopoietin-2 and VEGF-A pathways with faricimab, the first bispecific antibody designed for intraocular use, may promote vascular stability translating into increased durability and improved long-term outcomes beyond anti-VEGF alone for nAMD.[7,9] The Phase 3 TENAYA (NCT03823287) and LUCERNE (NCT03823300) trials were designed to compare the efficacy, durability, and safety of faricimab with aflibercept in patients with nAMD.

Methods

TENAYA and LUCERNE are identical, Phase 3, randomized, double-masked, active comparator–controlled, 112-week studies of faricimab in nAMD. Eligible patients were ≥50 years of age, had treatment-naive nAMD, choroidal neovascularization (CNV) lesion of any type, and BCVA of 78 to 24 ETDRS letters. Patients were randomized 1:1 to receive faricimab 6.0 mg up to every 16 weeks (Q16W) after 4 initial doses or aflibercept 2.0 mg every 8 weeks (Q8W) after 3 initial doses. Patients in the faricimab arm were assessed for protocol-defined disease activity at Weeks 20 and 24. Patients with no active disease at Weeks 20 and 24 received Q16W dosing through Week 60; patients with active disease at Week 24 received every-12-weeks (Q12W) dosing, and those with active disease at Week 20 received Q8W dosing until Week 60. The primary efficacy endpoint was noninferiority of faricimab up to Q16W to aflibercept Q8W in mean change in BCVA from baseline averaged over Weeks 40, 44, and 48. Secondary endpoints include the proportion of patients on faricimab Q16W, Q12W, and Q8W regimens; proportion of patients gaining or avoiding a loss of ≥15 ETDRS letters from baseline, and change in central subfield thickness (CST) from baseline by spectral domain OCT (SD-OCT). Safety was assessed by the incidence and severity of ocular and non-ocular adverse events.

Results

In total, 1329 patients with nAMD were enrolled in TENAYA (*N* = 671) and LUCERNE (*N* = 658). Baseline characteristics were generally well balanced across treatment arms. Both trials met their primary endpoint of noninferiority in mean change in BCVA from baseline averaged over Weeks 40, 44, and 48 with faricimab up to Q16W (+5.8 and +6.6 ETDRS letters in TENAYA and LUCERNE, respectively) compared with aflibercept Q8W (+5.1 and +6.6 ETDRS letters in TENAYA and LUCERNE, respectively). Notably, 79.7% (TENAYA) and 77.8% (LUCERNE) of patients in the faricimab up to Q16W arm were on ≥Q12W dosing intervals at Week 48, with 45.7% and 44.9% of patients in TENAYA and LUCERNE, respectively, on a Q16W dosing interval. Reductions in CST from baseline averaged over Weeks 40, 44, and 48 with faricimab up to Q16W (–136.8 and –137.1 µm in TENAYA and LUCERNE, respectively) were comparable with aflibercept Q8W (–129.4 and –130.8 µm in TENAYA and LUCERNE, respectively). In both trials, faricimab was well tolerated; intraocular inflammation event rates were low and on average reported in 2.0% and 1.2% of patients for faricimab and aflibercept, respectively. There were no investigator-reported cases of vasculitis or occlusive retinitis in either study.

Discussion

TENAYA and LUCERNE met their primary endpoint, with consistent and reproducible results across both trials. Faricimab administered at up to Q16W demonstrated comparable vision gains to aflibercept Q8W in patients with nAMD, with meaningful reductions in CST, and was well tolerated. Almost 80% of faricimab-treated patients were on fixed-dosing intervals of ≥Q12W, and ~45% were on fixed-dosing intervals of Q16W at Week 48, suggesting that the durability potential of dual Ang-2 and VEGF-A inhibition could result in sustained efficacy through extended durability, reducing the overall treatment burden while maximizing vision gains.

References

1. AAO PPP Retina/Vitreous Committee, Hoskins Center for Quality Eye Care. Age-related macular degeneration PPP 2019. American Academy of Ophthalmology, ONE Network website. www.aao.org/preferred-practice-pattern/age-related-macular-degeneration-ppp.

2. Holz FG, Tadayoni R, Beatty S, et al. Multi-country real-life experience of anti-vascular endothelial growth factor therapy for wet age-related macular degeneration. *Br J Ophthalmol*. 2015; 99(2):220-226.

3. Ciulla TA, Hussain RM, Pollack JS, Williams DF. Visual acuity outcomes and anti-vascular endothelial growth factor therapy intensity in neovascular age-related macular degeneration patients: a real-world analysis of 49 485 eyes. *Ophthalmol Retina*. 2020; 4(1):19-30.

4. Prenner JL, Halperin LS, Rycroft C, Hogue S, Williams Liu Z, Seibert R. Disease burden in the treatment of age-related macular degeneration: findings from a time-and-motion study. *Am J Ophthalmol*. 2015; 160(4):725-31 e1.

5. Heier JS, Singh RP, Wykoff CC, et al. The angiopoietin/Tie pathway in retinal vascular diseases: a review. *Retina* 2021; 41(1):1-19.

6. Joussen AM, Ricci F, Paris LP, Korn C, Quezada-Ruiz C, Zarbin M. Angiopoietin/Tie2 signalling and its role in retinal and choroidal vascular diseases: a review of preclinical data. *Eye (Lond)*. 2021; 35(5):1305-1316.

7. Regula JT, Lundh von Leithner P, Foxton R, et al. Targeting key angiogenic pathways with a bispecific CrossMAb optimized for neovascular eye diseases. *EMBO Mol Med*. 2016; 8(11):1265-1288. [Erratum in *EMBO Mol Med*. 2019; 11(5):e10666.]

8. Foxton RH, Uhles S, Grüner S, Revelant F, Ullmer C. Efficacy of simultaneous VEGF-A/ANG-2 neutralization in suppressing spontaneous choroidal neovascularization. *EMBO Mol Med*. 2019; 11(5):e10204.

9. Khanani AM, Patel SS, Ferrone PJ, et al. Efficacy of every four monthly and quarterly dosing of faricimab vs ranibizumab in neovascular age-related macular degeneration: the STAIRWAY phase 2 randomized clinical trial. *JAMA Ophthalmol*. 2020;138(9):964-972. [Erratum in *JAMA Ophthalmol*. 2020;138(9):1006.]

Recalcitrant Fluid in Neovascular AMD: Why Does It Not Go Away?

David Sarraf MD

NOTES

What's Wrong With Step Therapy for Wet AMD?

Paul Sternberg Jr MD

I. What is step therapy?

A. Step therapy, also called "step protocol" or a "fail first" requirement, is an approach to prescription by an insurance company, pharmacy benefit manager, or insurance company.

B. It is a type of prior authorization requirement that is intended to control the costs and risks posed by prescription drugs.

C. Step therapy means trying less expensive options before "stepping up" to drugs that cost more.

II. Why is step therapy being considered for the management of wet AMD?

A. It is well known that bevacizumab is a less expensive option than ranibizumab or aflibercept.

B. Initiation of bevacizumab as first drug prior to "stepping up" to other agents would save considerable dollars.

III. Why is step therapy opposed by some retina specialists?

A. Financial margin greater for ranibizumab > aflibercept >>>>> bevacizumab

B. Limits treatment options for clinicians and for patients

C. Compounded bevacizumab may have limited availability in some areas.

D. Concerns about safety of compounded bevacizumab

IV. What's wrong with step therapy?

A. Little to no evidence of significant clinical benefit to patients of more expensive agents vs. bevacizumab as first line

B. No demonstration of long-term vision detriments from step therapy

C. Comparable rates of infection: Since improving standards for compounding pharmacies, there have been no recent cohorts of infected compounded bevacizumab.

D. Comparable rates of systemic side effects

E. Significant reduction in financial responsibility for patients with bevacizumab

F. Significantly reduced cost to society with step therapy

Neovascular AMD Panel Discussion

Panel Moderator: Sunir J Garg MD FACS

Panelists: Karl G Csaky MD, Jean-Pierre Hubschman MD, Mathew W MacCumber MD PhD, and Daniel F Martin MD

NOTES

Clinically Actionable Mutations in 1700 Patients From the Collaborative Ocular Oncology Group Using a Uveal Melanoma Next-Generation Sequencing Panel

J William Harbour MD

Introduction

Uveal melanoma (UM) is the most common primary malignancy of the eye and one of the most deadly forms of cancer. Half of patients with UM are at significant risk for developing metastatic disease based on the molecular composition of the primary tumor. The most fundamental subdivision of UMs is into Class 1 versus Class 2, most accurately and reliably based on gene expression profiling (GEP) using a 12-gene panel and associated machine learning algorithm that has been prospectively validated and widely used for the past decade. The GEP/PRAME system is strongly associated with key driver mutations, with most Class 2 UMs having mutational inactivation of the tumor suppressor BAP1, and many Class 1 tumors having mutations in either SF3B1 or EIF1AX. Class 1/SF3B1-mutant tumors tend to be PRAME-positive and have an intermediate risk of metastasis, whereas Class 1/EIF1AX-mutant tumors tend to be PRAME-negative and have a low risk of metastasis. BAP1, SF3B1, and EIF1AX ("BSE") mutations not only provide prognostic information; they may also indicate therapeutically actionable vulnerabilities. UMs with BAP1 loss show susceptibility to inhibitors of histone deacetylase (HDAC), poly(ADP-ribose) polymerase 1 (PARP), and DNA methylation, whereas UMs with SF3B1 mutations may be vulnerable to treatment with bromodomain-containing protein 9 (BRD9) stabilizers and may be more responsive to immune therapies. Most UMs also harbor initiating mutations in a member of the Gaq signaling pathway, including GNAQ, GNA11, PLCB4, and CYSLTR2. These mutations are largely mutually exclusive and appear to be required for tumor initiation but not for malignant transformation or metastasis. Even though Gaq mutations are not of prognostic value, they are relatively uncommon in other cancer types, such that they can help confirm the uveal melanocytic nature of a tumor, as opposed to a simulating lesion. Further, these mutations may render tumors "addicted" to certain growth signaling pathways, such as the MAPK, PI3K/AKT, FAK, and Hippo pathways, which can be pharmacologically targeted using drugs in clinical use. Since BSE and Gaq mutations may be of clinical value, we created a highly robust targeted next-generation sequencing (NGS) panel for analyzing these mutations from a single fine needle biopsy sample that can also be used for GEP/PRAME testing.

Observations

The UM-targeted NGS mutation panel has undergone extensive analytical validation, provides sequencing coverage much deeper than generic off-the-shelf mutation panels, and is now available for clinical use. The panel is undergoing prospective clinical evaluation by the Collaborative Ocular Oncology Group Study No. 2 (COOG2), comprising 25 leading ocular oncology centers in the United States and Canada (https://coog.life). Enrollment was closed at 1715 patients. The first cohort to be analyzed were 245 small UMs with thickness ≤3 mm. In this cohort, GEP was Class 1, 71.8%; Class 2, 28.2%. The following mutations were found: GNAQ (57.6%), GNA11 (39.6%), BAP1 (25.7%), EIF1AX (28.2%), SF3B1 (15.9%), PLCB4 (1.6%), and CYSLTR2 (1.6%). Class 1 GEP was strongly associated with mutations in SF3B1 and EIF1AX ($P < .001$ for both). Of Class 1 UMs, 42.6% harbored neither an SF3B1 nor an EIF1AX mutation. Class 2 GEP was strongly associated with BAP1 mutations ($P < .001$).

Conclusions

Our custom targeted NGS mutation panel allows UM-associated driver mutations to be detected with great precision, even from small tumors, using a single small-gauge needle biopsy that can also be used for GEP/PRAME testing. While SF3B1 and EIF1AX mutations are strongly associated with Class 1 GEP (high specificity), they are not present in many Class 1 tumors (low sensitivity). Likewise, BAP1 mutations are strongly associated with Class 2 GEP (high specificity) but are not detected in ~10% of UM, likely because of the well-known difficulty detecting all possible deleterious mutations in large tumor suppressor genes such as BAP1. Thus, GEP continues to be superior to mutational analysis and other methods for prognostication, but mutational analysis can identify potentially actionable mutations in the vast majority of cases. Longer follow-up and ongoing analysis of the entire COOG2 cohort will reveal how best to incorporate this mutation panel into precision medicine for patients with UM.

Selected Readings

1. Cai L, Paez-Escamilla M, Walter SD, et al. Gene expression profiling and PRAME status versus tumor-node-metastasis staging for prognostication in UM. *Am J Ophthalmol*. 2018; 195:154-160.
2. Decatur CL, Ong E, Garg N, et al. Driver mutations in UM: associations with gene expression profile and patient outcomes. *JAMA Ophthalmol*. 2016; 134:728-733.
3. Faiao-Flores F, Emmons MF, Durante MA, et al. HDAC inhibition enhances the in vivo efficacy of MEK inhibitor therapy in UM. *Clin Cancer Res*. 2019; 25:5686-5701.
4. Feng X, Arang N, Rigiracciolo DC, et al. A platform of synthetic lethal gene interaction networks reveals that the GNAQ UM oncogene controls the Hippo pathway through FAK. *Cancer Cell*. 2019; 35:457-472 e455.
5. Field MG, Durante MA, Anbunathan H, et al. Punctuated evolution of canonical genomic aberrations in UM. *Nat Commun*. 2018; 9:116.

6. Goncalves Avezedo J, Emmons MF, Faiao-Flores F, et al. Decitabine limits escape from MEK inhibition in UM. *Pigment Cell Melanoma Res*. 2019; 33:507-514.
7. Harbour JW, Onken MD, Roberson ED, et al. Frequent mutation of BAP1 in metastasizing UMs. *Science* 2010; 330:1410-1413.
8. Harbour JW, Roberson ED, Anbunathan H, Onken MD, Worley LA, Bowcock AM. Recurrent mutations at codon 625 of the splicing factor SF3B1 in UM. *Nat Genetics*. 2013; 45:133-135.
9. Inoue D, Chew GL, Liu B, et al. Spliceosomal disruption of the non-canonical BAF complex in cancer. *Nature* 2019; 574:432-436.
10. Kuznetsoff JN, Owens DA, Lopez A, et al. Dual screen for efficacy and toxicity identifies HDAC inhibitor with distinctive activity spectrum for BAP1-mutant UM. *Mol Cancer Res*. 2020; 19:215-222.

Retinal Toxicity of Novel Cancer Treatments

Jasmine H Francis MD

I. Introduction
   A. Recent expansion of cancer treatments beyond conventional chemotherapy to targeted agents and immunotherapy
   B. Brief review of retinal toxicity of conventional chemotherapy

II. Targeted Agents
   A. Mechanism of drugs
   B. Cancers treated with drugs
   C. Retinal toxicity
      1. Clinical findings
      2. Clinical course of toxicity
      3. Treatment
      4. Implications and prognosis of toxicity

III. Targeted Agents: Small Molecule Inhibitors
   A. Mechanism of drugs
   B. Cancers treated with drugs
   C. Retinal toxicity
      1. Clinical findings
      2. Clinical course of toxicity
      3. Treatment
      4. Implications and prognosis of toxicity

IV. Immunotherapy
   A. Mechanism of drugs
   B. Cancers treated with drugs
   C. Retinal toxicity
      1. Clinical findings
      2. Clinical course of toxicity
      3. Treatment
      4. Implications and prognosis of toxicity

V. Conclusion

Table 1

Class	Drugs	Mechanism	Retinal Side Effects
Biologics			
	interferon alpha 2b	• Recombinant protein connects adaptive and innate immune response. • Apoptotic, anti-proliferative, anti-angiogenic, and immunoregulatory properties	Cotton wool spots, retinal hemorrhage, central retinal vein occlusion
	denileukin diftitiox	• Fusion protein targets IL-2 receptors, delivers diphtheria toxin intracellularly. • Inhibits intracellular protein synthesis, leading to cell death	Macular pigment changes, decreased vision
	trastuzumab	Binds human epidermal growth factor receptor 2 protein (HER-2)	Macular edema, hemorrhages, and exudates
Small molecule inhibitors			
	infigratinib erdafitinib	FGFR inhibitor, which can also work downstream to inhibit the MAPK pathway	Foci of serous retinal detachments, retinal vein occlusion
	vemurafenib dabrafenib encorafenib	BRAF kinase inhibitor that inhibits specific mutated forms of BRAF in cancer cells	Uveitis, central macula edema
	trametinib cobimetinib binimetinib selumetinib PD-325901	Inhibits MEK kinases, which are downstream factors in the MAPK pathway that regulates cell growth, proliferation, and differentiation	Foci of serous retinal detachments, retinal vein occlusion
	ulixertinib	Inhibits ERK kinases, which are downstream factors in the MAPK pathway	Foci of serous retinal detachments, retinal vein occlusion, cystoid changes in the outer nuclear layer
	crizotinib	Inhibits anaplastic lymphoma kinase (ALK)	Light/dark adjustment deficits
	imatinib	Bcr-Abl tyrosine kinase inhibitor	Retinal hemorrhages, neovascularization, central macula edema, optic disc edema
Immunotherapy			
	ipilimumab	Monoclonal antibody targeting cytotoxic T-lymphocyte antigen-4 (CTLA-4)	Panuveitis, uveitis, vitritis, optic nerve edema, serous retinal detachment, choroidopathy, CNV, Vogt-Koyanagi-Harada–like syndrome
	pembrolizumab nivolumab cemiplimab dostarlimab	Programmed death protein 1 (PD-1) inhibitor	Panuveitis, uveitis, vitritis, optic nerve edema, vasculitis, cystoid macula edema, hypotony, uveal effusion syndrome, immune retinopathy, Vogt-Koyanagi-Harada–like syndrome
	atezolizumab avelumab durvalumab	Programmed death ligand (PD-L1) inhibitor	Panuveitis, uveitis, vitritis, optic nerve edema, vasculitis, acute macula neuroretinopathy, uveal effusion syndrome

Oncology Panel Discussion

Panel Moderator: Timothy G Murray MD MBA

Panelists: Jasmine H Francis MD, Ivana K Kim MD, Tara A McCannel MD, and Prithvi Mruthyunjaya MD

NOTES

Guidelines for Managing Diabetic Macular Edema Based on Visual Acuity

Neil M Bressler MD

I. Central Subfield Not Thickened on OCT (approximately <300 µm)

A. Typical management: Observe per data from DRCR Retina Network Protocol R: Only around 15% of eyes developed center-involved diabetic macular edema (DME); visual acuity was usually very good when center-involved DME first developed.

B. If eye subsequently develops central subfield thickening (CST) on OCT (approximately 300 µm or more), then management depends on visual acuity (VA) at time center-involved DME first is noted, as explained in remainder of outline below.

II. Center-Involved DME and VA 20/32 or Worse

A. Anti-VEGF leads to greater average gain in VA compared with focal/grid laser or corticosteroids combined with focal/grid laser, per DRCR Retina Network Protocol I. When comparing across agents, see below for data from DRCR Retina Network Protocol T.

B. When VA 20/32 to 20/40, on average, 1 anti-VEGF agent (among aflibercept, 0.3-mg ranibizumab, and repackaged bevacizumab [not approved by the FDA for this indication]) does not lead to superior VA outcomes compared with another agent.

C. When VA is 20/50 or worse, on average, aflibercept leads to superior VA outcomes compared with bevacizumab at 1 and 2 years, and compared with ranibizumab at 1 year and over 2 years (where data over 2 years represents area under the curve) when adjusting for baseline VA and for multiple analyses.

D. These outcomes based on mean VA change (the primary outcome in Protocol I and T, and a sensitive way of comparing groups) are supported by secondary outcomes for gaining 15 or more letters from baseline at 1 year and over 2 years.

E. DRCR Retina Network DME Treatment Regimen, based on 3 principles:

1. Initially, 6 monthly injections unless 20/20 and OCT "normal" after 2 consecutive injections within 6 months

2. Thereafter, continue anti-VEGF only if *either* OCT CST or VA improves or worsens compared with the last 2 injections (ie, no injection if *both* OCT CST and VA are stable); but, consider adding focal/grid laser to residual, stable DME if treatable lesions per DRCR Retina Network focal/grid laser treatment regimen (available at www.drcr.net). Beyond 1 year, extend follow-up to 2, then 4 months.

3. Resume anti-VEGF if VA or OCT worsens from DME (improvement or worsening defined as ≥5 letter change (~1 Snellen line), or, ≥10% CST change on OCT, monthly, until stable on VA and OCT CST again.

F. DRCR Retina Network DME Treatment Regimen associated with sustained VA gains with reduced median number of injections from baseline in Protocol I but not Protocol T

1. Injections in Protocol I from baseline to 0.5, 1, 2, 3, 4, and 5 years: 6, 3, 3, 2, 1, 0 compared with injections in Protocol T from baseline to 0.5, 1, and 2 years: 6, 3, 5

2. Protocol T extension: Participants returned to standard care after 2-year visit, and 2/3 returned for a 5-year visit.

a. 32% had no injection; 68% had 1 to 32 injections from Year 2 to Year 5 (median: 4).

b. Mean VA declined 4.7 letters from Year 2 to Year 5; similar decline noted if baseline VA 20/32 to 20/40 or baseline VA 20/50 or worse; similar decline noted regardless of anti-VEGF agent used for entire group or by agent used or by agent used within 20/32 to 20/40 or 20/50 or worse cohort.

c. Decline from Year 2 to 5 in Protocol T but not in Protocol I not due to different number of median injections, or number of lasers; could be lack of systematic follow-up in Protocol T during Years 2 to 5 or missing data or some other factor yet to be identified.

III. Center-Involved DME and Good VA (20/25 or Better)

A. Three alternative therapies tested in Protocol V – one not superior to another, including:

1. Observe and add aflibercept if VA declines

2. Focal/grid laser and add aflibercept if VA declines

3. Aflibercept per DRCR Retina Network DME Treatment Regimen, except focal/grid laser optional beyond 6 months for persistent, stable DME

B. Rescue aflibercept for VA worsening (loss of ≥10 letters from baseline at any visit, or 5-9 letters at 2 consecutive visits), not OCT CST worsening; if only OCT CST worsening, decrease follow-up interval to minimum of 1 month.

C. 85% are 20/25 or better at 2 years in Protocol V (starting at 20/25 or better) with median of 8 injections over 2 years, compared with 71% who start 20/32 to 20/40 or 44% who start 20/50 or worse in Protocol T with median of 14 injections over 2 years.

IV. Conclusion

Monitor eyes with no DME or non-central DME periodically for development of center-involved DME. Try to identify central-involved DME while VA is good and follow Protocol V DME Management Regimen depending on patient's values and needs; if VA is 20/32 or worse, follow Protocol T DME Treatment Regimen.

V. References

See Protocols I, R, T, and V at www.drcr.net then click on "Information about the Network" and then click on "Publication List" and scroll to specific protocol.

Faricimab Diabetic Macular Edema Phase 3 Trials

One-Year Efficacy, Safety, and Durability in the Phase 3 YOSEMITE and RHINE Trials

Jeffrey S Heier MD

Background

Diabetic macular edema (DME) is a multifactorial disease that arises as a result of vascular instability, which is characterized by vascular leakage, neovascularization, pericyte loss, and inflammation. Both angiopoietin-2 (Ang-2) and vascular endothelial growth factor (VEGF) levels are upregulated under pathological conditions and together drive DME pathology.[1,2] Although anti-VEGF treatment is the current standard of care,[3] it addresses only one aspect of the disease. Furthermore, the need for ongoing, often monthly injections is burdensome for patients, caregivers, and the health-care system. Real-world data suggest that patients with DME receive fewer anti-VEGF injections in clinical practice compared with randomized clinical trials.[2] Thus, best-achievable visual responses to treatment with anti-VEGF agents are difficult to achieve and maintain in clinical practice.[4]

Faricimab, the first bispecific antibody designed for intraocular use, targets Ang-2 and VEGF-A. Data from the Phase 2 BOULEVARD trial (NCT02699450) and preclinical models suggest that dual inhibition of the Ang-2 and VEGF-A pathways with faricimab may reduce inflammation and vascular leakage, promote vascular stability, and improve long-term outcomes beyond anti-VEGF alone in DME.[5,6] The Phase 3 YOSEMITE (NCT03622580) and RHINE (NCT03622593) trials were designed to compare the efficacy, durability, and safety of faricimab versus aflibercept dosed per label in patients with DME.

Methods

YOSEMITE and RHINE are identical, randomized, double-masked, active comparator–controlled, 100-week, Phase 3 trials of faricimab in treatment-naive and previously anti-VEGF–treated patients with DME. Eligible patients were aged ≥18 years, with center-involving DME (central subfield thickness [CST] ≥ 325 µm) and BCVA of 73 to 25 Early Treatment Diabetic Retinopathy (ETDRS) letters (~20/40–20/320 Snellen equivalent). Patients were randomized 1:1:1 to receive faricimab 6.0 mg every 8 weeks (Q8W) after 6 initial Q4W doses, faricimab 6.0 mg per personalized treatment interval (PTI) after 4 initial Q4W doses, or aflibercept 2.0 mg Q8W after 5 initial Q4W doses. The PTI algorithm is a protocol-driven regimen based on the treat-and-extend (T&E) concept. Patients randomized to the PTI arm received faricimab at intervals determined by an automated algorithm based on prespecified BCVA and CST criteria applied at active dosing visits; dosing intervals could be adjusted in 4-week increments (minimum interval: Q4W; maximum interval: Q16W).

The primary efficacy endpoint was mean change in BCVA from baseline at 1 year, averaged over Weeks 48, 52, and 56. Noninferiority in the intention-to-treat (ITT) population followed by superiority in treatment-naive patients was assessed separately for each faricimab arm against aflibercept. Secondary endpoints included the proportion of patients with ≥2-step ETDRS Diabetic Retinopathy Severity Scale (DRSS) improvement from baseline at Week 52, proportion of patients gaining or avoiding a loss of ≥15 ETDRS letters from baseline at 1 year, change in CST from baseline over time, proportion of patients with absence of protocol-defined DME over time, proportion of patients with the presence/absence of intra- and subretinal fluid over time, and proportion of patients in the PTI arm on Q4W, Q8W, Q12W, or Q16W dosing at Week 52. Safety was assessed by the incidence and severity of ocular and non-ocular adverse events.

Results

In total, 1891 patients with DME were enrolled in YOSEMITE (N = 940) and RHINE (N = 951). Baseline characteristics were well balanced across treatment arms. Both trials met the primary endpoint; mean BCVA gains from baseline at 1 year with faricimab Q8W (+10.7 and +11.8 ETDRS letters in YOSEMITE and RHINE, respectively) or faricimab PTI up to Q16W (+11.6 and +10.8 ETDRS letters in YOSEMITE and RHINE, respectively) were noninferior to aflibercept Q8W (+10.9 and +10.3 ETDRS letters in YOSEMITE and RHINE, respectively). Notably, more than 70% of patients achieved Q12W or Q16W PTI dosing at Week 52 (73.8% in YOSEMITE and 71.1% in RHINE), and more than 50% of patients achieved Q16W treatment at Week 52 (52.8% in YOSEMITE and 51.0% in RHINE). In treatment-naive patients, mean BCVA gains at 1 year were consistent with the ITT population, and no faricimab arm showed superiority to aflibercept. Mean change in CST over 1 year consistently favored faricimab over aflibercept. Similarly, absence of protocol-defined DME (CST < 325 µm) was achieved by more patients treated with faricimab versus aflibercept: at Week 56, 82% to 90% of faricimab-treated patients across YOSEMITE and RHINE compared with 65% to 73% of aflibercept-treated patients. More patients treated with faricimab had absence of intraretinal fluid compared to aflibercept at the time points analyzed (Weeks 16, 48, 52, and 56), with 33% to 48% of faricimab-treated patients compared to 22% to 29% of aflibercept-treated patients.

Rates of absence of subretinal fluid were high and similar across all 3 treatment arms in both studies. The rates of ≥2-step ETDRS-DRSS improvement at Week 52 were consistent with both faricimab Q8W and PTI dosing regimens across both trials and treatment arms. Faricimab was well tolerated in YOSEMITE and RHINE. Rates of intraocular inflammation were low, on average reported in 1.3% and 0.6% of patients for faricimab and aflibercept, respectively. There were no reported cases of retinal vasculitis or occlusive retinitis in either study at the time of primary analyses.

Discussion

The YOSEMITE and RHINE studies met their primary endpoints, with BCVA gains at 1 year with faricimab Q8W or PTI up to Q16W noninferior to aflibercept Q8W in patients with DME. Patients treated with faricimab showed improvements in anatomic outcomes, with consistently greater CST improvements and absence of DME and absence of intraretinal fluid compared with aflibercept-treated patients. Faricimab was well tolerated, and adverse events of intraocular inflammation were low. YOSEMITE and RHINE are the first registrational trials in DME to evaluate a fully automated protocol-driven T&E regimen using the PTI. More than half of all patients in the faricimab PTI arms were on a Q16W treatment interval at 1 year, showing that faricimab—the first bispecific antibody in ophthalmology that inhibits both Ang-2 and VEGF-A—provides the potential for extended dosing of Q16W in a majority of patients with DME while maintaining vision outcomes.

References

1. Joussen AM, Ricci F, Paris LP, Korn C, Quezada-Ruiz C, Zarbin M. Angiopoietin/Tie2 signalling and its role in retinal and choroidal vascular diseases: a review of preclinical data. *Eye (Lond)*. 2021; 35(5):1305-1316.
2. Heier JS, Singh RP, Wykoff CC, et al. The angiopoietin/TIE pathway in retinal vascular diseases. *Retina* 2021; 41(1):1-19.
3. AAO PPP Retina/Vitreous Committee, Hoskins Center for Quality Eye Care. Diabetic retinopathy PPP 2019. Accessed May 5, 2021. www.aao.org/preferred-practice-pattern/diabetic-retinopathy-ppp.
4. Ciulla TA, Pollack JS, Williams DF. Visual acuity outcomes and anti-VEGF therapy intensity in diabetic macular oedema: a real-world analysis of 28 658 patient eyes. *Br J Ophthalmol*. 2021;105(2):216-221.
5. Regula JT, von Leithner PL, Foxton R, et al. Targeting key angiogenic pathways with a bispecific CrossMAb optimized for neovascular eye diseases. *EMBO Mol Med*. 2016; 8(11):1265-1288. [Erratum in Regula JT, von Leithner PL, Foxton R, et al. *EMBO Mol Med*. 2019;11(5):e10666.]
6. Sahni J, Patel SS, Dugel PU, et al. Simultaneous inhibition of angiopoietin-2 and vascular endothelial growth factor-A with faricimab in diabetic macular edema: BOULEVARD Phase 2 randomized trial. *Ophthalmology* 2019; 126(8):1155-1170.

Let There Be Light: Photobiomodulation Therapy for Diabetic Macular Edema

(Protocol AE) from DRCR.net

Judy E Kim MD

Irradiation by light in the far-red (FR) to near-infrared (NIR) region of the spectrum (630-900 nm) is collectively termed "photobiomodulation" (PBM). It has been applied to tissues to produce beneficial cellular effects leading to improved outcomes at the cellular, systemic, and clinical level in a wide range of disease states. The driving mechanism behind these benefits suggests that the mitochondrial enzyme cytochrome C oxidase is a key photoacceptor of light in the FR to NIR spectral range. PBM has been shown to increase mitochondrial energy generation through ATP, replication, density, and activity and increases in RNA and protein synthesis. It has been shown to restore the function of damaged mitochondria, upregulate the production of cytoprotective factors, decrease inflammation, and prevent cell death. FR light has been found to inhibit production of the proinflammatory cytokines IFN-γ and TNF-α and to upregulate anti-inflammatory cytokines IL-4 and IL-10 in experimental autoimmune encephalomyelitis.

PBM has been applied clinically in the treatment of soft tissue injuries and acceleration of wound healing for more than 50 years. In addition to wound healing, FR to NIR light has been reported to be beneficial in a variety of conditions including recovery from ischemic injury to the heart, treatment of gingival incisions, peripheral nerve repair after trauma, and treatment of acute soft tissue injuries. The FDA approved the use of low-light therapy for carpal tunnel syndrome in 2003.

Limited clinical studies show high potential for the use of PBM for ocular diseases. Ivandic and colleagues have shown clinical improvements in patients with amblyopia, retinitis pigmentosa, and AMD after treatment with PBM. In subjects with AMD, treatment with a laser diode aimed at the macular area improved visual acuity in both dry and wet AMD. No changes in visual acuity were seen in the control group, and there were no reports of any adverse effects among PBM-treated patients. The Toronto and Oak Ridge PBM Studies for Dry Age-Related Macular Degeneration (TORPA I and II) presented evidence for clinical benefits after PBM in patients with dry AMD, including improvements in BCVA and contrast sensitivity and anatomical reductions in drusen volume.

The LIGHTSITE I study investigated the efficacy and safety of PBM treatment in subjects with dry AMD. Thirty subjects (46 eyes) were treated with the Valeda Light Delivery System, wherein subjects underwent 2 series of treatments (3 times per week for 3-4 weeks) over 1 year. PBM-treated subjects showed a BCVA mean letter score gain of 4 letters immediately after each treatment series at Month 1 and Month 7. Approximately 50% of PBM-treated subjects showed improvement of ≥5 letters versus 13.6% in sham-treated subjects at Month 1.

PBM has been evaluated in 2 small clinical studies of treatment for diabetic macular edema (DME). Tang et al reported the results of a nonrandomized, consecutive case series that evaluated PBM for non–center involving DME involving 4 patients with bilateral edema who were treated in 1 eye while the fellow eye served as the untreated control. After treatment for 160 s per day (9 J/cm^2) for 2 to 9 months, thickened areas on spectral domain OCT were reduced by a mean of 20% (±11.7%) in the treated eyes, and mean change in the untreated eyes was –3% (±8%).

Kim et al conducted a randomized prospective study in 10 patients with treatment-resistant DME, randomized to either standard treatment with continued anti-VEGF alone or anti-VEGF plus PBM. Although the sample size is small, the findings show a reduction in DME and an improvement in VA following NIR-PBM (ARVO 2017 presentation).

A Phase 3 clinical trial (CLEOPATRA) examined light-at-night delivered by sleep masks as a noninvasive intervention to prevent the progression of diabetic retinopathy and DME. It is important to note key differences between the mechanism of action of retinal exposure to FR (670 nm) light and retinal exposure to blue-green (505 nm) light used in the CLEOPATRA trial. Arden and colleagues showed that that blue-green (505 nm) light may mitigate the complications of diabetic retinopathy by modulating the metabolic activity of the retina. Their studies are based on evidence that dark-adaptation exacerbates hypoxia in the diabetic retina, acting as a powerful stimulus for the overproduction of VEGF and other less well understood factors. Several small clinical trials have shown that the prevention of dark adaptation ameliorates clinical signs of diabetic retinopathy. The outcome of the CLEOPATRA trial was negative, showing that the 505-nm light mask did not confer long-term therapeutic benefit on non–center involving diabetic macular edema.

A Pilot Study Evaluating Photobiomodulation Therapy for Diabetic Macular Edema (Protocol AE) from DRCR.net

The number of patients with diabetes is expected to grow globally. Given the potentially large numbers of patients with center-involved DME and good vision, evaluation of a low-risk, noninvasive, and low-cost treatment alternative to anti-VEGF in this group of patients is warranted. Therefore, Diabetic Retinopathy Clinical Research Retina Network (DRCR.net) performed a randomized clinical trial evaluating the effect of PBM compared with sham on central subfield thickness (CST) in eyes with central-involved DME and good vision of 20/20 to 20/25. This study was conducted as a pilot study to determine whether the conduct of a pivotal trial has merit based on an anatomic outcome and provides information on outcome measures needed to design a pivotal trial.

There are 2 phases of the study. The primary outcome will be evaluated at the end of Phase 1 (4 months). At the 4-month

visit, participants will switch to the alternative treatment. The switch serves 2 purposes:

1. To provide participants originally assigned to sham the opportunity to receive the active treatment and
2. To explore the post-switch effects within treatment group. No statistical comparisons will be performed in Phase 2 to compare treatment groups.

The following are some key aspects of the trial:

Primary efficacy outcome

Mean change in CST from baseline at 4 months

Key secondary efficacy outcomes

Treatment group comparisons

- Mean change in retinal volume from baseline at 4 months
- Percentage of eyes with CST below OCT machine- and gender-specific threshold for DME at 4 months
- Percentage of eyes receiving alternative treatment for DME by 4 months
- Percentage of eyes with a ≥5 letter loss in visual acuity
- Patient compliance
- Exploratory assessment of treatment effect after the device is stopped or started

Key inclusion criteria

- Age ≥18 years
- Type 1 or type 2 diabetes
- At least 1 eye with each of the following:
  - Best corrected E-ETDRS visual acuity letter score ≥79 (ie, 20/25 or better)
  - Ophthalmoscopic evidence of central-involved DME in study eye confirmed by CST on spectral domain OCT:
    - Zeiss Cirrus: ≥290 µm in women, and ≥305 µm in men
    - Heidelberg Spectralis: ≥305 µm in women, and ≥320 µm in men

Key exclusion criteria

- No history of prior laser, surgical, intravitreous, or peribulbar treatment for DME or DR in the study eye within the prior 12 months.
- *If more than 12 months ago, no more than 4 prior intraocular injections*

Enrollment will be limited to a maximum of 15% of the planned sample size with any history of anti-VEGF treatment and a maximum of 15% with any history of PRP.

Randomization

Random assignment (1:1) to photobiomodulation (PBM) or sham

Trial length

The trial lasts 8 months for each participant (primary outcome at 4 months)

The primary outcome has been analyzed and will be presented at this meeting. Publication will be forthcoming.

References

1. Albarracin R, Eells J, Valter K. Photobiomodulation protects the retina from light-induced photoreceptor degeneration. *Invest Ophthalmol Vis Sci*. 2011; 52:3582-3592.
2. Anders JJ, Geuna S, Rochkind S. Phototherapy promotes regeneration and functional recovery of injured peripheral nerve. *Neurol Res*. 2004; 26(2):233-239.
3. Arden GB, Jyothi S, Hogg CH, Lee YF, Sivaprasad S. Regression of early diabetic macular oedema is associated with prevention of dark adaptation. *Eye (Lond)*. 2011; 25(12):1546-1554.
4. Arden GB, Gunduz MK, Kurtenbach A, et al. A preliminary trial to determine whether prevention of dark adaptation affects the course of early diabetic retinopathy. *Eye (Lond)*. 2010; 24(7):1149-1155.
5. Cotler HB. A NASA discovery has current applications in orthopaedics. *Curr Orthop Pract*. 2015; 26(1):72-74.
6. Eells JT, Henry MM, Summerfelt P, et al. Therapeutic photobiomodulation for methanol-induced retinal toxicity. *Proc Natl Acad Sci U S A*. 2003; 100:3439-3444.
7. Eells JT, Henry MM, Summerfelt P, et al. Therapeutic photobiomodulation for methanol-induced retinal toxicity. *Proc Natl Acad Sci U S A*. 2003; 100(6):3439-3444.
8. Eells JT, Wong-Riley MT, VerHoeve J, et al. Mitochondrial signal transduction in accelerated wound and retinal healing by near-infrared light therapy. *Mitochondrion* 2004; 4:559-567.
9. Eells JT, Gopalakrishnan S, Valter K. Near-infrared photobiomodulation in retinal injury and disease. *Adv Exp Med Biol*. 2016; 854:437-441.
10. Gkotsi D, Begum R, Salt T, et al. Recharging mitochondrial batteries in old eyes: near infra-red increases ATP. *Exp Eye Res*. 2014; 122:50-53.
11. Gigo-Benato D, Geuna S, Rochkind S. Phototherapy for enhancing peripheral nerve repair: a review of the literature. *Muscle Nerve*. 2005; 31(6):694-701.
12. Ivandic BT, Ivandic T. Low-level laser therapy improves vision in patients with age-related macular degeneration. *Photomed Laser Surg*. 2008; 26:241-245.
13. Ivandic BT, Ivandic T. Low-level laser therapy improves visual acuity in adolescent and adult patients with amblyopia. *Photomed Laser Surg*. 2012; 30:167-171.
14. Ivandic BT, Ivandic T. Low-level laser therapy improves vision in a patient with retinitis pigmentosa. *Photomed Laser Surg*. 2014; 32:181-184.
15. Markowitz SN, Devenyi RG, Munk MR, et al. A double-masked, randomized, sham-controlled, single-center study with photobiomodulation for the treatment of dry age-related macular degeneration. *Retina* 2020; 40(8):1471-1482.
16. Merry GF, Munk MR, Dotson RS, et al. Photobiomodulation reduces drusen volume and improves visual acuity and contrast sensitivity in dry age-related macular degeneration. *Acta Ophthalmol*. 2017; 95:e270-e277.
17. Muili KA, Gopalakrishnan S, Meyer SL, Eells JT, Lyons JA. Amelioration of experimental autoimmune encephalomyelitis in C57BL/6 mice by photobiomodulation induced by 670 nm light. *PLoS One*. 2012; 7(1):e30655.
18. Munk MR, Markowitz SN, Devenyi R, et al. Final analysis of LIGHTSITE I: a double-masked, randomized, sham-controlled study with photobiomodulation in dry age-related macular degeneration subjects. ARVO 2018 Abstract 2415-C0081.

19. Neiburger EJ. Rapid healing of gingival incisions by the helium-neon diode laser. *J Mass Dent Soc*. 1999; 48(1):8-13, 40.

20. Oron U, Yaakobi T, Oron A, et al. Low-energy laser irradiation reduces formation of scar tissue after myocardial infarction in rats and dogs. *Circulation* 2001; 103(2):296-301.

21. Rustia M, Cardesa A. Ganglioneuromas in hamsters. *Acta Neuropathol*. 1975; 32(4):325-331.

22. Seme MT, Summerfelt P, Henry MM, Neitz J, Eells JT. Formate-induced inhibition of photoreceptor function in methanol intoxication. *J Pharmacol Exp Ther*. 1999; 289(1):361-370.

23. Tang J, Du Y, Lee CA, et al. Low-intensity far-red light inhibits early lesions that contribute to diabetic retinopathy in vivo and in vitro. *Invest Ophthalmol Vis Sci*. 2013; 54:3681-3690.

24. Tang J, Herda AA, Kern TS. Photobiomodulation in the treatment of patients with non-center-involving diabetic macular edema. *Br J Ophthalmol*. 2014; 98(8):1013-1015.

Use of Ultrawide-field Fluorescein Angiography in the Management of Diabetic Retinopathy

Barbara Blodi MD

I. Introduction to Ultrawide-field (UWF) Fluorescein Angiography (FA)

Use of UWF imaging:

A. UWF color and FA use increasing steadily: in 2020 PAT survey, majority of retina specialists (72% U.S. and 57% worldwide) have access to widefield imaging (*N* = 1011).

B. Two companies with UWF FA systems commercially available and FDA approved

1. Optos PLC; Dunfermline, Scotland
2. Clarus, Carl Zeiss Meditec AG

C. Other UWF imaging systems include UWF OCT and UWF OCT angiography (not discussed).

II. Clinical Uses for UWF FA

A. Detection of proliferative diabetic retinopathy (PDR)

1. Simultaneous view of central and peripheral retina allows for easier detection of disc and retinal neovascularization.
2. Small areas of neovascularization are more readily identified in mid and far periphery on UWF FA systems than with standard FA imaging systems.

B. Evaluation of leakage

1. Area of macular edema may be more extensive than that seen on standard FA.
2. Unusual patterns of leakage in mid and far periphery may be present on UWF FA.

C. Detection of nonperfusion

1. Retinal ischemia in eyes with non-PDR (NPDR) and PDR can be simultaneously identified in central and peripheral retina.
2. Areas of nonperfusion much more commonly seen, both in eyes with NPDR and PDR

III. Use of UWF FA in Clinical Trials and Other Research Purposes

A. Identification of PDR for eligibility in a trial: UWF FA is useful in PDR prevention trials where presence of any retinal neovascularization at baseline is exclusionary (Regeneron Panorama, DRCR Protocol W).

B. Evaluation of retinal ischemia

1. Standard FA: ETDRS study group concluded that FA did not significantly add to the predictive power of color fundus photographs.[1]
2. Quantification of nonperfusion has improved with UWF FA; area of capillary loss reported as percent involvement (ischemic index) or area measurement in millimeter squared with correction factor for peripheral warping
3. Nonperfusion may not improve after anti-VEGF treatment.[2]

IV. Future Applications of UWF FA

A. To assist in development of deep learning algorithms for nonperfusion[3]

B. To improve ETDRS scale

1. UWF FA may add to the predictive value of the current ETDRS scale in predicting progression to PDR.
2. UWF FA may be particularly useful in eyes after anti-VEGF treatment.

References

1. ETDRS Research Group. Fluorescein angiographic risk factors for progression of diabetic retinopathy. ETDRS Report No. 13. *Ophthalmology* 1991; 98(5 suppl):834-840.
2. Couturier A, Rey PA, Erginay A. Widefield OCT-angiography and fluorescein angiography assessments of nonperfusion in diabetic retinopathy and edema treated with anti-vascular endothelial growth factor. *Ophthalmology* 2019; 126:1685-1694.
3. Nunez de Rio JM, Sen Y, Rasheed R, et al. Deep learning-based segmentation and quantification of retinal capillary non-perfusion on ultra-widefield retinal fluorescein angiography. *J Clin Med*. 2020; 9:2537.

Lapses in Care When Treating Proliferative Diabetic Retinopathy: What Have We Learned?

Susan B Bressler MD

Introduction

The Diabetic Retinopathy Study (1976) showed that panretinal photocoagulation (PRP) was an effective treatment for proliferative diabetic retinopathy (PDR), with ≥50% reduction in rates of severe vision loss compared to observation. Protocol S of the DRCR Retina Network demonstrated that intravitreal ranibizumab provided vision outcomes that were noninferior to PRP at 2 years in eyes with PDR, even when ranibizumab was given to the PRP group for center-involved diabetic macular edema (DME) with vision loss. These results appeared to be maintained through 5 years (2018). The UK-based CLARITY Study (2017) showed that aflibercept achieved superior vision outcomes when compared to PRP at 1 year in eyes with PDR wherein anti-VEGF was not permitted in the PRP group if DME developed. Potential advantages of ranibizumab relative to PRP include less visual field loss, reductions in incident vision-impairing DME, less frequent vitrectomy, and fewer retinal detachments through 2 years. As such, there is sound rationale to consider anti-VEGF therapy to manage PDR.

Administration of anti-VEGF therapy for PDR requires more frequent and regular visits than that required when PRP is the sole treatment modality, although follow-up through at least 5 years following PRP also is needed to detect new or recurrent PDR warranting additional PRP, onset of DME with vision loss or nonclearing vitreous hemorrhage, or traction retinal detachment. Clinical trial protocols used 4-6 monthly injections to foster regression or stabilization of neovascularization. Once accomplished, this was followed by regular monitoring visits, initially at 4-week intervals with extension to 8 weeks and then 16 weeks, to assess PDR activity and determine need for repeat anti-VEGF injection and shortening of interval between monitoring visits. Among the 66% of surviving Protocol S participants who completed the 5-year exam, the median number of visits was 43 and 21 for the ranibizumab and PRP groups, respectively.

Many factors require consideration when selecting which treatment modality to use for PDR, including compliance with follow-up schedule, costs, convenience (work absences or transportation or travel distance), DME status, and comorbidities. PDR patients often have a variety of comorbid conditions, elevated HbA1c levels, and potentially less compliance with medical care than DM populations without PDR. These issues add to concern about selection of anti-VEGF therapy and its need for more frequent visits and treatment than PRP to avoid the blinding complications of PDR.

Lapses in Care: Potential Definitions

To my knowledge, no consistent definition of lapses in care has been accepted universally by ophthalmologists monitoring patients with PDR. Most publications provide retrospective descriptions of lapses in care among patients being managed in the clinical practice setting with PRP, anti-VEGF, or both modalities, with variable length of follow-up ranging from 6 months to 5 years.

Definitions currently considered include no office visit for >6 months (16%-61% have lapse in care when followed ≤5 years); no office visit for >12 months (10%-25% have lapse in care when followed ≤4 years). Definitions have not given detailed consideration to the individualized recommended interval from the last completed visit.

Strengths of these reports

Data generated from clinical practice may reflect behaviors in the PDR cohort that most clinicians are presently managing.

Limitations

Heterogenous treatment interventions, heterogenous recommendations for timing of treatments and monitoring schedules, variable resources to track and encourage compliance with visit schedule. Lack of standardized visual acuity (VA) measurements. Selection bias in choosing treatment modality.

Can we improve upon these definitions?

The DRCR Retina Network is attempting to improve upon these definitions in the context of the Protocol S database in which treatment and visit schedules were determined prospectively. Should length of lapse be considered relative to the disease activity level when the lapse occurs? Should shorter lapses in care be evaluated to understand effects on outcomes and explore whether there are "safe" periods of monitoring/treatment interruption that may provide some flexibility in the follow-up schedule? Development of consensus definitions is important to facilitate consistent reporting of the problem and comparisons in different settings, which in turn may lead to improved strategies and better vision outcomes.

Lapses in Care: Why Does It Matter?

The concern is compromise in the desired goals of therapy: (a) avoid blindness or vision loss (≤20/200, ≥6-line loss) and (b) avoid anatomic progression (clinically relevant vitreous hemorrhage, retinal detachment, neovascular glaucoma, incident DME or exacerbation of DME). This applies to patients treated with either PRP, anti-VEGF, or both interventions.

Studies report that some patients present with irreversible VA loss and/or vision-threatening disease progression after a lapse in care; however, without a control group the strength of the association between lapse in care and disease progression is challenging to interpret. DRCR Retina Network is evaluating whether vision and anatomic outcomes are affected by lapses in care among Protocol S patients assigned to ranibizumab. Note: Factors that may be associated with poor visit compliance may also be associated with poor VA or anatomic outcomes in patients with PDR (ie, lower level of initial VA or more advanced diabetic retinopathy severity or other socioeconomic factors).

Management of Patients With PDR Can Include Measures to Mitigate Risk of Lapses in Care

Suggested prevention strategies

- Emphasize critical importance of timely follow-up at baseline and all follow-up exams.
- Implement office practices to monitor and facilitate adherence to the visit schedule for this patient population, irrespective of treatment modality. This may require additional resources (ie, social work, mobility assistance, text messages).
- Identify baseline factors associated with lapses in care to further intensify efforts in the highest-risk population.
- Identify when lapses are most likely to occur in follow- up and concentrate on those intervals.
- Determine if there are signals in visit adherence that increase probability of longer lapses in care or complete loss to follow-up and target those individuals.

Identification of baseline factors that are favorably associated with visit adherence may provide intervention strategies to be applied to the higher-risk population.

Additional Challenges in Studying Lapses in Care

While prospective studies minimize bias, there is selection bias to identify participants likely to adhere to treatment schedules and planned methods to facilitate participant retention. Furthermore, eyes with the longest lapses in care are those that fail to ever return, and their outcomes (functional and anatomic) or receipt of care elsewhere remain unknown. These outcomes may not be universally poor. Given that Protocol S reported about 34% loss to follow-up at 5 years, a comparison of the consequences of lapses in care on treatment outcomes between the anti-VEGF and the PRP arms is problematic. Nevertheless, this remains an important issue to probe further to understand the incidence and reasons behind lapses in care to optimize delivery and outcomes of two very effective PDR therapies.

Selected Readings

1. Gross JG, Glassman AR, Liu D, et al. Five-year outcomes of panretinal photocoagulation vs intravitreous ranibizumab for proliferative diabetic retinopathy: a randomized clinical trial. *JAMA Ophthalmol.* 2018; 136(10):1138-1148.
2. Obeid, A, Gao XG, Ali FS, et al. Loss to follow-up in patient with proliferative diabetic retinopathy after panretinal photocoagulation or intravitreal anti-VEGF injections. *Ophthalmology* 2018; 125:1386-1392.
3. Abdelmotaal H, Ibrahim W, Sharaf M, Abdelazeem K. Causes and clinical impact of loss to follow-up in patients with proliferative diabetic retinopathy. *J Ophthalmol.* Epub ahead of print 2020 Feb 8. doi.org/10.11552020/7691724.

Panretinal Photocoagulation: A Rational Guide for Its Use

David N Zacks MD PhD

Abstract

Panretinal photocoagulation (PRP) has been a mainstay treatment for neovascular diseases of the retina for over 50 years. In recent years, the introduction of anti-VEGF therapy has called into question the utility of PRP and whether this procedure has any role in the modern ophthalmic practice. In this talk, I will review the data on the use of PRP in retinal vascular disease, particularly diabetic retinopathy and vascular occlusive disease. The main learning objectives are to be able to describe the mechanism by which PRP exerts its beneficial effects, recognize the indications for PRP, and provide a rational algorithm for deciding when to perform this procedure—alone or in combination with anti-VEGF therapy.

DRCR Protocol W: Prophylactic Use of Anti-VEGF Treatment

A Randomized Trial of Intravitreous Anti-VEGF for Prevention of Vision-Threatening Complications of Diabetic Retinopathy (Protocol W)

Raj K Maturi MD and the DRCR Retina Network

I. Background

A. Eyes with moderate to severe nonproliferative diabetic retinopathy (NPDR) are at high risk for progressing to proliferative diabetic retinopathy (PDR) or developing vision-threatening complications such as center-involved diabetic macular edema (CI-DME).

B. Intravitreal anti-VEGF therapy is an effective first-line treatment for PDR and CI-DME.[1-4] Effectiveness as treatment for NPDR in the absence of vision-threatening complications is less clear.

C. Primary objective: To determine efficacy of aflibercept (Eylea, Regeneron) anti-VEGF injections compared with sham in preventing eyes with NPDR from developing PDR or CI-DME with vision loss. And if so, was there an associated visual benefit at 2 years?

II. Methods

A. Study design: randomized multicenter clinical trial conducted by the DRCR Retina Network

1. 64 sites in U.S. and Canada
2. 399 eyes (328 participants) were enrolled and followed for at least 2 years (study completion at 4 years).
3. Eyes were stratified by diabetic retinopathy severity score (DRSS) and randomly assigned in a 1:1 ratio to:
   a. Aflibercept (2 mg)
   b. Sham
4. Primary outcome: Development of PDR or CI-DME with vision loss through when the last 2-year visit was completed

B. Major inclusion criteria

1. ≥18 years old with type 1 or type 2 diabetes
2. Severe NPDR in at least 1 eye (determined by investigator)
3. DRSS between 43 and 53 on reading center grading. After 9 months of recruitment the lower cutoff was modified from 47B.
4. No evidence of neovascularization on fluorescein angiography within the 7 modified ETDRS fields
5. BCVA letter score ≥79 (20/25 or better)
6. No history of DME/DR treatment within 12 months and ≤4 prior injections
7. No prior panretinal photocoagulation

C. Major exclusion criteria: CI-DME on clinical exam or a central subfield thickness greater than machine and sex OCT thresholds

D. Treatment

1. Prevention injections (either aflibercept or sham)
   a. Given at every visit before 2 years (baseline and 1, 2, 4, 8, 12, 16, and 20 months)
   b. Given at visits after 2 years (24, 28, 32, 36, 40 and 44 months) if eyes had worse than mild NPDR (>level 35) on clinical exam
2. If PDR or CI-DME developed, then aflibercept treatment was initiated and the DRCR Retina Network algorithms for anti-VEGF retreatment were followed.[5,6]

III. Results

A. Baseline participant characteristics

1. Age: Median = 57 years in aflibercept, 56 years in sham
2. Female: 42% in aflibercept, 43% in sham
3. Type 2 diabetes: 94% in aflibercept, 43% in sham
4. Race/ethnicity
   a. White: 46% in aflibercept, 43% in sham
   b. Black/African American: 15% in aflibercept, 16% in sham
   c. Hispanic or Latino: 31% in aflibercept, 34% in sham
   d. Asian: 5% in aflibercept, 5% in sham
   e. Other: 2% in aflibercept, 2% in sham

B. Baseline ocular characteristics

1. Visual acuity: Median = 88 letter score in aflibercept, 88 letter score in sham (Snellen equivalents of 20/20)
2. OCT central subfield thickness (Spectralis machine equivalents): Median = 283 μm in aflibercept, 283 μm in sham
3. Prior DME treatment: 10% in aflibercept, 11% in sham

C. Study treatments through 2 years

1. At least 1 aflibercept injection for PDR /DME: 4% in aflibercept, 19% in sham
2. Total number of aflibercept injections: Mean (SD) = 8.0 (1.2) in aflibercept, 1.1 (2.7) in sham

D. Efficacy

1. Development of PDR or CI-DME with vision loss
   a. 2-year cumulative probability: 16.3% in aflibercept, 43.5% in sham
   b. Adjusted hazard ratio* = 0.32 (97.5% CI, 0.21-0.50; $P < .001$)
2. Development of PDR
   a. 2-year cumulative probability: 13.5% in aflibercept, 33.2% in sham
   b. Adjusted hazard ratio* = 0.34 (97.5% CI, 0.21-0.55; $P < .001$)
3. Development of CI-DME with vision loss
   a. 2-year cumulative probability: 4.1% in aflibercept, 14.8% in sham
   b. Adjusted hazard ratio* = 0.36 (97.5% CI, 0.17-0.77; $P = .002$)
4. Visual acuity change from randomization to 2 years
   a. Mean (SD) = –0.9 (5.8) letters in aflibercept, –2.0 (6.1) letters in sham
   b. Adjusted mean difference = 0.5 letters (97.5% CI, –1.0 to 1.9; $P = .47$)

*Adjustments for DR severity at the screening visit, study eye laterality, and correlation between eyes of participants with 2 study eyes

E. Safety outcomes

1. Endophthalmitis: 2% in aflibercept, 0 in sham
2. Any retinal detachment: 1% in aflibercept, 1% in sham

IV. Conclusions

A. Aflibercept injections reduce development of vision-threating complications.

B. Preventive treatment did not confer visual acuity benefit at 2 years compared with observation plus aflibercept if complications developed.

References

1. Diabetic Retinopathy Clinical Research Network. Randomized trial evaluating ranibizumab plus prompt or deferred laser or triamcinolone plus prompt laser for diabetic macular edema. *Ophthalmology* 2010; 117(6):1064-1077 e1035.
2. Diabetic Retinopathy Clinical Research Network; Wells JA, Glassman AR, et al. Aflibercept, bevacizumab, or ranibizumab for diabetic macular edema. *N Engl J Med*. 2015; 372(13):1193-1203.
3. Writing Committee for the Diabetic Retinopathy Clinical Research Network; Gross JG, Glassman AR, Jampol L, et al. Panretinal photocoagulation vs intravitreous ranibizumab for proliferative diabetic retinopathy: a randomized clinical trial. *JAMA*. 2015; 314(20):2137-2146.
4. Sivaprasad S, Prevost AT, Vasconcelos JC, et al. Clinical efficacy of intravitreal aflibercept versus panretinal photocoagulation for best corrected visual acuity in patients with proliferative diabetic retinopathy at 52 weeks (CLARITY): a multicentre, single-blinded, randomised, controlled, Phase 2b, non-inferiority trial. *Lancet* 2017; 389(10085):2193-2203.
5. Gross JG, Glassman AR, Liu D, et al. Five-year outcomes of panretinal photocoagulation vs intravitreous ranibizumab for proliferative diabetic retinopathy: a randomized clinical trial. *JAMA Ophthalmol*. 2018; 136(10):1138-1148.
6. Wells JA, Glassman AR, Ayala AR, et al. Aflibercept, bevacizumab, or ranibizumab for diabetic macular edema: two-year results from a comparative effectiveness randomized clinical trial. *Ophthalmology* 2016; 123(6):1351-1359.

Diabetes Panel Discussion

Panel Moderator: Jennifer K Sun MD

Panelists: Lloyd P Aiello MD PhD, Gregg T Kokame MD, Susanna S Park MD PhD, and John A Wells III MD

NOTES

Update on the International Classification of ROP, 3rd Edition (ICROP3)

RV Paul Chan MD MBA, Michael F Chiang MD, Graham E Quinn MD MSCE, Alistair R Fielder FRCP, and Susan R Ostmo MS on behalf of the ICROP3 Committee

I. History of ICROP

A. 1984: Original consensus about disease classification (23 ophthalmologists from 11 countries). Used to facilitate first multicenter clinical treatment study (CRYO-ROP) → first demonstration that this blinding disease could be treated successfully

B. 1987: Expanded to include classification of retinal detachment

C. 2005: Revisited for new knowledge and imaging technology (eg, pre-plus disease, aggressive posterior ROP)

II. Why do we need a new ICROP3 classification system now?

A. Concerns about subjectivity in critical elements of ROP classification (particularly plus disease)

B. Innovations in imaging → raising questions about validity of traditional ophthalmoscopic tenets, and potential future improvements in classification using quantitative methods

C. Major advances in treatment (particularly anti-VEGF agents) are creating new challenges regarding classification of post-treatment regression and reactivation.

D. Recognition that patterns of ROP in some regions of the world are reminiscent of disease descriptions in the 1950s (eg, Reese, King, Owens) → may require acknowledgment

III. Who is involved in ICROP3?

A. International representation: 34 ophthalmologists from 6 continents

B. Executive Committee

1. Chair: Michael F Chiang MD; Vice-Chair: Graham E Quinn MD MSCE

2. International Pediatric Ophthalmology & Strabismus Council Chair of ROP Committee: RV Paul Chan MD MBA

3. Subcommittee Chairs: Graham E Quinn MD (acute phase), Alistair R Fielder FRCP (regression/reactivation), Michael F Chiang MD (imaging)

C. Breadth of backgrounds: 20 retina/14 pediatric ophthalmology, 22 male/12 female

IV. What are new elements in the ICROP3 compared to previous efforts?

A. Posterior zone II: Definition of an intermediate "posterior zone II" region at the margin between zone I and zone II, which is associated with higher risk of developing severe retinopathy than disease located in more peripheral retina

B. Temporal notch: The committee introduced the term "notch" to describe an incursion by the ROP lesion of 1 to 2 clock hours along the horizontal meridian into a more posterior zone than the remainder of the retinopathy.

C. Stage 5 ROP: Definition of further subcategorization of stage 5 ROP

D. Aggressive ROP (A-ROP)

1. Recognition that there is a continuous spectrum of disease from mild ROP to A-ROP at either end, and that these entities may not be distinct

2. Recognition that there may be differences in disease appearance in regions with limited resources

E. Plus disease: Recognition of further categorization of the spectrum of retinal vascular abnormality in ROP, with sample images showing the continuum from normal vasculature to plus disease, thereby permitting clinicians to stratify the risk of severe disease with enhanced precision

F. Regression and reactivation

1. Definition and description of nomenclature representing ROP regression and its sequelae, whether spontaneous or following laser and anti-VEGF treatment

2. Definition and description of nomenclature representing categorization of ROP reactivation following treatment. This includes the recommendation that reactivation of peripheral ROP lesions should utilize the modifier "reactive" (eg, "reactive stage 2").

G. Long-term ROP sequelae

1. Description of long-term ROP disease sequelae

2. Patients with a history of premature birth, even without a history of ROP, exhibit a spectrum of ocular abnormalities that may lead to permanent sequelae

Selected Readings

1. Chiang MF, Quinn GE, Fielder AR, et al. International Classification of Retinopathy of Prematurity, Third Edition. *Ophthalmology*. Epub ahead of print 2021 Jul 8. doi: 10.1016/j.ophtha.2021.05.031.

2. Repka MX. A revision of the International Classification of Retinopathy of Prematurity. *Ophthalmology*. Epub ahead of print 2021 Jul 29. doi: 10.1016/j.ophtha.2021.07.014.

Emerging Therapies for Pediatric Retinal Diseases

Antonio Capone Jr MD

I. Introduction

Therapeutic advances in the last decade have added options to the armamentarium for the management of pediatric retinal diseases, in some cases where none previously existed. We are in the beginning of the era of genetically informed medicine. This presentation will provide an overview of ongoing therapeutic initiatives in the pediatric retina space.

II. Artificial Intelligence and Deep Learning

III. Pharmacotherapy

IV. Stem-Cell Therapy

V. Gene Therapy

VI. Summary

Disparities in Geographic Access to U.S. ROP Treatment Centers

Yoshihiro Yonekawa MD, Rebecca R Soares MD, Louis Cai MD, Annika Samuelson BS, Charles Huang BS, Christopher Andrews, John Hinkle, Samir Patel, David Musch, Rebecca Vartanian, and Cagri Besirli MD

Purpose

To identify geographic and socioeconomic variables predictive of residential proximity to neonatal intensive care units (NICUs) treating retinopathy of prematurity (ROP).

Methods

This cross-sectional epidemiologic analysis crosslinked data from 3 public datasets and data from a nationwide survey of NICU directors regarding ROP treatment. Using origin-destination cost-matrix analyses, we identified the travel time from each U.S. census tract to the nearest NICU offering treatment of ROP. Primary outcomes were driving time >60 minutes and driving distance >60 miles. Using multivariable analysis, we then identified census-tract level socioeconomic predictors of driving time.

Results

Rural residents had to travel a significantly longer time to reach any ROP treatment (103.23 ± 55.47 minutes vs. 42.68 ± 41.40 minutes). The longest time traveled was over 8 hours for those in Lincoln County, Montana. Mean travel time to the nearest NICU offering anti-VEGF in addition to laser was longer than mean travel time to laser for both rural (308.93 ± 218.32 mins vs. 108.07 ± 57.53, $P < .0001$) and urban (258.02 ± 207.57 vs. 51.78 ± 50.99, $P < .0001$) census tracts. Residents were more likely to travel >60 minutes to the nearest ROP treatment center if they lived in census tracts that were rural [adjusted odds ratio (aOR), 1.33; 95% CI, 1.29-1.37; $P < .0001$] or had higher percentages of the population living in the West 1.11 (1.09-1.12; $P < .0001$ and South 1.19 (1.18-1.20; $P < .0001$) compared to the Northeast. Residents also had a greater travel burden if they lived in census tracts with a greater percentage of the population living at or below federal poverty level (fourth quartile vs. first quartile, 1.14 (1.12-1.16), $P < .0001$. In contrast, counties with higher percentages of births <1500 g (aOR 0.90; 0.90-0.90; $P < .0001$) were less likely to travel >60 minutes.

Conclusions

Although counties with higher incidences of very-low birth weight infants were closer to ROP treatment, residents living in low-income, less educated, and more non-white census tracts had significantly greater travel burdens to the nearest ROP treating NICU.

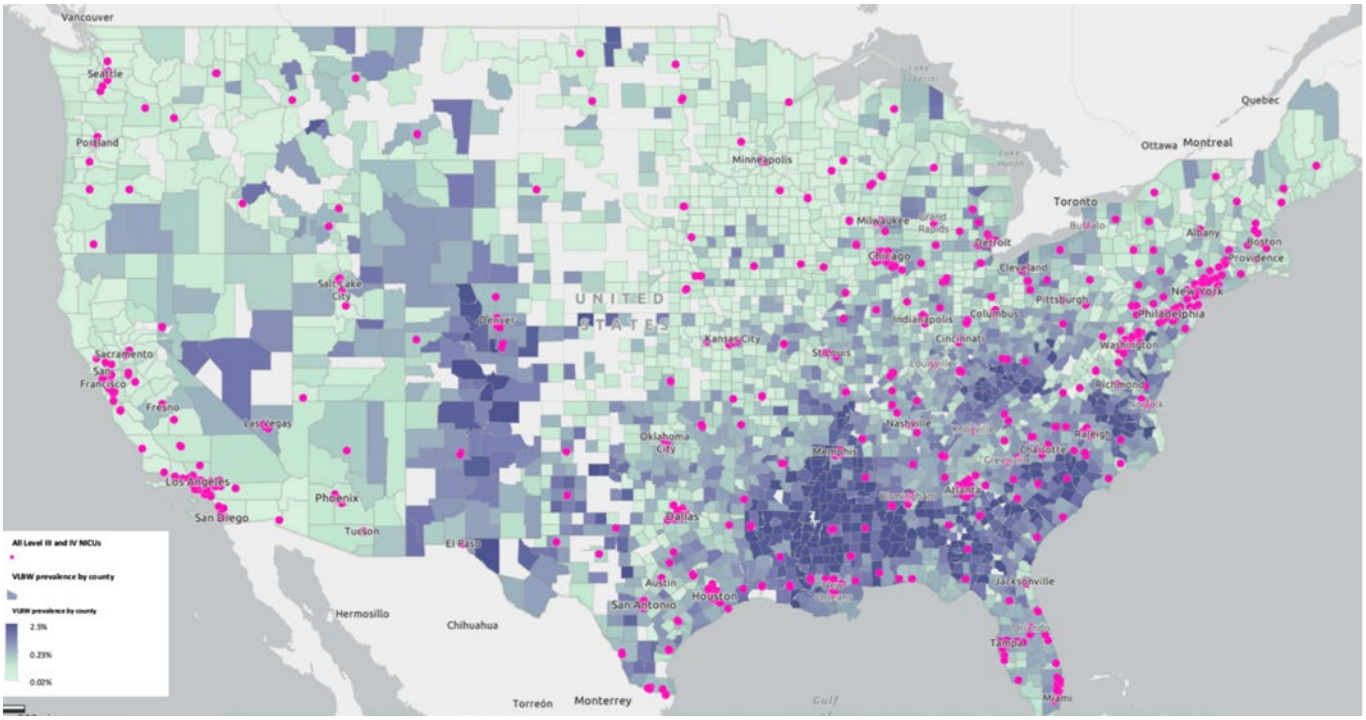


Figure 1

References

1. Kong L, Fry M, Al-Samarraie M, et al. An update on progress and the changing epidemiology of causes of childhood blindness worldwide. *J AAPOS*. 2012; 16:501-507.
2. Lad EM, Nguyen TC, Morton JM, Moshfeghi DM. Retinopathy of prematurity in the United States. *Br J Ophthalmol*. 2008; 92:320-325.
3. Ludwig CA, Chen TA, Hernandez-Boussard T, et al. The epidemiology of retinopathy of prematurity in the United States. *Ophthalmic Surg Lasers Imaging Retina*. 2017; 48:553-562.
4. Vartanian RJ, Besirli CG, Barks JD, et al. Trends in the screening and treatment of retinopathy of prematurity. *Pediatrics* 2017; 139.
5. American Academy of Pediatrics Committee on Fetus and Newborn. Levels of neonatal care. *Pediatrics* 2012; 130:587-597.
6. USDA ERS. Rural-Urban Commuting Area Codes. www.ers.usda.gov/data-products/rural-urban-commuting-area-codes.aspx. Accessed August 4, 2020.
7. United States Department of Health and Human Services (US DHHS), Centers for Disease Control and Prevention (CDC), National Center for Health Statistics (NCHS), Division of Vital Statistics. Natality public-use data 2016-2019. CDC WONDER Online Database, October 2020. http://wonder.cdc.gov/natality-expanded-current.html. Accessed Jan. 10, 2021.

Pediatric Retina Panel Discussion

Panel Moderator: G Baker Hubbard MD

Panelists: Audina M Berrocal MD, Cagri G Besirli MD, R V Paul Chan MD, and Yoshihiro Yonekawa MD

NOTES

Where Do We Stand With Cell-Based Therapy for Retinal Diseases?

Rajesh C Rao MD

NOTES

Delivery Strategies for Gene and Cell Therapies in Retinal Disease

Allen C Ho MD

Intravitreal injection (clinic based) is familiar and is utilized in several gene and cell therapy programs; some designer gene therapy viral vectors are able penetrate the retinal internal limiting membrane to transfect retinal cells, and this specificity may not be needed to transfect other cells (for example, ciliary epithelium) exposed to the vitreous cavity. Subretinal delivery (OR based) affords direct surgical access to target retinal pigment epithelial (RPE) cells and retinal cells/photoreceptors. Direct access to these cell targets in the subretinal space may be important for certain gene and cell therapies for retinal diseases; subretinal delivery may be achieved with a transvitreal approach or a suprachoroidal to subretinal strategy. Some programs are investigating suprachoroidal delivery (clinic based) for delivery of gene and cell therapies to the posterior segment. 2017 FDA approval of subretinal delivery of voretigene for RPE65 Leber congenital amaurosis and RPE65 retinitis pigmentosa, as well as evidence from other clinical trials for other retinal degenerations and neovascular AMD, have established the feasibility and safety of transvitreal subretinal delivery after pars plana vitrectomy. Improving gene and cell therapies requires not only refining viral vectors, transgenes, and cell lines but also improving surgical delivery techniques and designing new instrumentation to achieve these goals.

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

I. Intravitreal Injection

   A. Office based

   B. Familiar and high safety profile

II. Transvitreal Subretinal Delivery After Pars Plana Vitrectomy

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

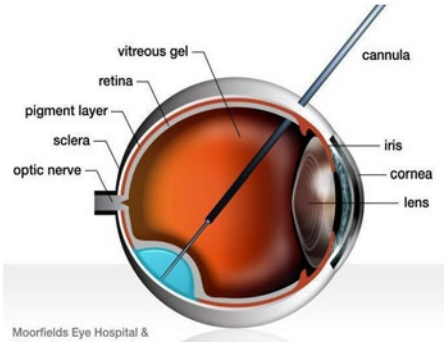


Figure 1. Credit: Moorfields Eye Hospital.

   A. OR procedure

      1. Conduct preoperative site planning and load MicroDose injection syringe connected to Viscous Fluid Injection system and 41-gauge flexible cannula to prepare for delivery with no air bubbles.

      2. Test system to create drip from 41-gauge cannula (typically VFI @ 10-20 mmHg).

      3. Pars plana vitrectomy with posterior vitreous detachment induction

      4. 41-gauge cannula to subretinal space with simultaneous foot pedal injection (optional intraoperative OCT)

      5. MicroDose syringe allows measured subretinal volume, typically 100 µL to 250 µL.

      6. ± air–fluid exchange

   B. Instrumentation: improved control and precision with MicroDose Injection Kit

      1. 1 cc syringe: aspirate or back fill and remove air bubbles

      2. Adaptor to VFI system of vitrectomy machine for foot pedal control

      3. Low pressure setting to create drip rate from 41-gauge cannula

Figure 2

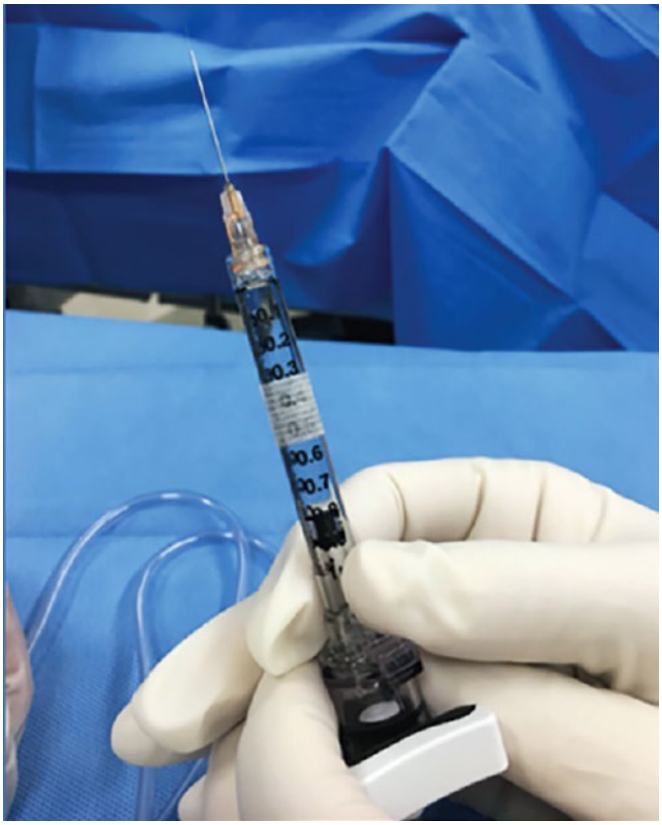


Figure 3

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

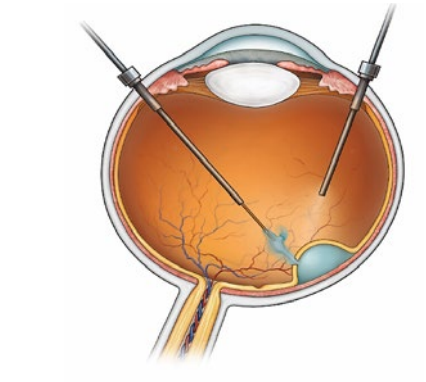


Figure 4

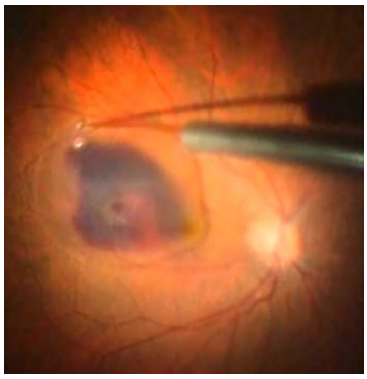


Figure 5

D. Cell therapies delivered on ultrathin sheet scaffolds
   1. Require larger retinotomies and specialized tools
   2. We may become the "new retina microtransplant surgeons."

Figure 6

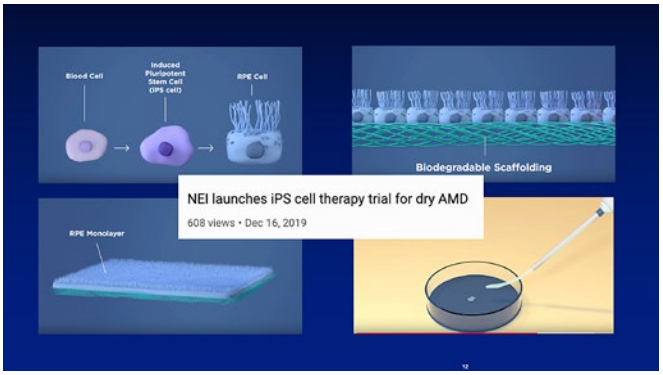


Figure 7

III. Transvitreal Subretinal Delivery Without Pars Plana Vitrectomy

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

IV. Ab Externo Suprachoroidal to Subretinal Delivery

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

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

1. Flexible suprachoroidal catheter inserted through sclerotomy
2. 38-gauge microadjustable advancing microcatheter can deliver saline or switch to intervention.

Figure 8

B. Ab externo suprachoroidal to subretinal procedure

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

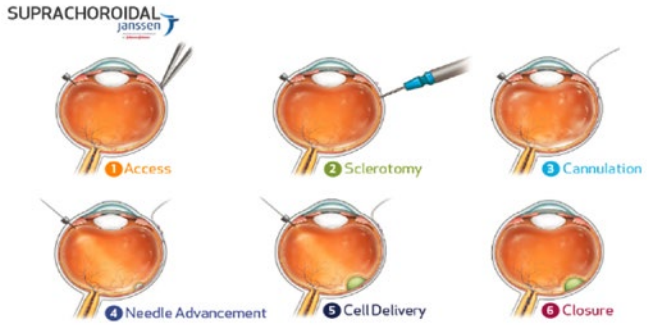


Figure 9

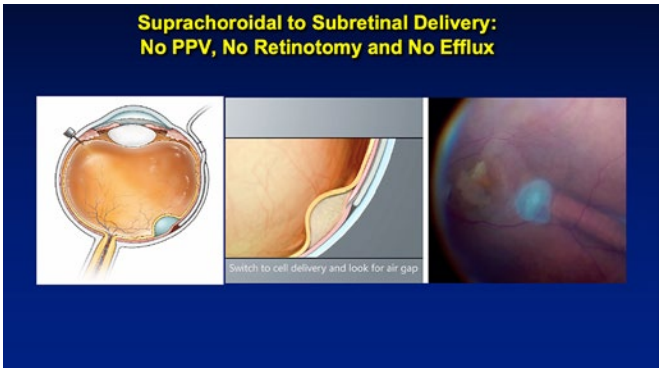


Figure 10

V. Preoperative and intraoperative imaging technology may improve subretinal delivery.

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

A. Intraoperative OCT may improve subretinal delivery accuracy.

B. Intraoperative OCT may improve subretinal dosing accuracy.

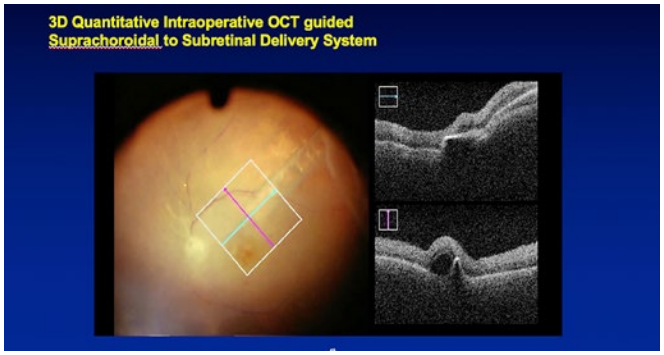


Figure 11

VI. Suprachoroidal injection is being explored to simplify delivery of gene, cell, and other retinal therapies.

A. Does not deliver to the subretinal space, but preclinical work suggests diffuse transfection of RPE and retinal cells even distal to injection site.

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

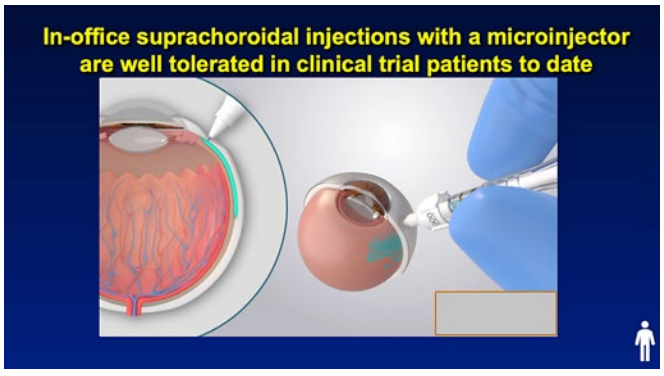


Figure 12

VII. Summary

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

References

1. Maguire AM, Simonelli F, Pierce EA, et al. Safety and efficacy of gene transfer for Leber's congenital amaurosis. *N Engl J Med*. 2008; 358:2240-2248.
2. Ho AC, Chang TS, Samuel M, Williamson P, Willenbucher RF, Malone T. Experience with a subretinal cell-based therapy in patients with geographic atrophy secondary to age-related macular degeneration. *Am J Ophthalmol*. 2017; 179:67-80.
3. Heier JS, Ho AC, Samuel MA, et al.; Prelude Study Group. Safety and efficacy of subretinally administered palucorcel for geographic atrophy of age-related macular degeneration: Phase 2b study. *Ophthalmol Retina*. 2020; 4(4):384-393.
4. Kashani AH, Uang J, Mert M, et al. Surgical method for implantation of a biosynthetic retinal pigment epithelium monolayer for geographic atrophy: experience from a Phase 1/2a study. *Ophthalmol Retina*. 2020; 4(3):264-273.
5. Schwartz SD, Regillo CD, Lam BL, et al. Human embryonic stem cell-derived retinal pigment epithelium in patients with age-related macular degeneration and Stargardt's macular dystrophy: follow-up of two open-label Phase 1/2 studies. *Lancet* 2015; 385(9967):509-516.
6. Xue K, Groppe M, Salvetti AP, MacLaren RE. Technique of retinal gene therapy: delivery of viral vector into the subretinal space. *Eye* 2017; 31:12308-1316.
7. Fischer MD, Hickey DG, Singh MS, MacLaren RE. Evaluation of an optimized injection system for retinal gene therapy in human patients. *Hum Gene Ther Methods*. 2016; 27:150-158.
8. Ding K, Shen J, Hafiz Z, et al. AAV8-vectored suprachoroidal gene transfer produces widespread ocular transgene expression. *J Clin Invest*. 2019; 129(11):4901-4911.
9. Yiu G, Chung SH, Mollhoff IN, et al. Suprachoroidal and subretinal injections of AAV using transscleral microneedles for retinal gene delivery in nonhuman primates. *Mol Ther Methods Clin Dev*. 2020; 16:179-191.
10. Ho AC, Wan C, Ciulla T. Suprachoroidal injections across species analyzed via multimodal imaging. *Invest Ophthalmol Vis Sci*. 2021; ARVO E-Abstract 3539577.

Drug and Gene Delivery Through the Suprachoroidal Space

Glenn Yiu MD PhD

Background

The suprachoroidal space is a potential space located between the choroid and sclera that usually becomes visible or accessible in the presence of ocular pathology. However, recent advances in enhanced-depth OCT imaging have enabled better visualization of this space, even under physiologic conditions.[1] Novel tools such as microneedles and microcatheters can access the suprachoroidal space to deliver drugs or viral vectors, although variations in the choroid-scleral interface, isolation from anterior segment structures, and adjacency to the high-flow choroidal vasculature impart unique pharmacokinetics to the suprachoroidal space.[2,3] Unlike intravitreal injections, suprachoroidal delivery of pharmacologic agents such as steroids has the potential to increase durability while reducing the risk of cataracts or IOP response.[4-6] Similarly, suprachoroidal injections of viral vectors or nanoparticles for gene therapy provide widespread transgene expression in contrast to subretinal and intravitreal delivery,[7-9] but the sequestration of viral particles outside the blood–retinal barrier may elicit host immune responses that are distinct from other modes of viral delivery.[10]

Outline

In this presentation, I review insights gained from imaging the suprachoroidal space using enhanced-depth OCT imaging and methods to access the suprachoroidal space such as microneedles or microcatheters. Next, I discuss results of recent clinical trials using suprachoroidal injection of steroid suspensions for treatment of macular edema associated with uveitis, retinal vein occlusions, and diabetes, including the potential benefits and challenges of this unique mode of ocular drug delivery. Finally, I present preclinical data from nonhuman primates comparing the delivery of viral vectors to the suprachoroidal space, as compared to intravitreal or subretinal injections, and explain the advantages and disadvantages of this mode of viral delivery in emerging gene therapy studies. Due to the unique location and biodistribution of drugs and vectors delivered to the suprachoroidal space, these exciting, early studies provide important implications for systemic impact and host immune responses after suprachoroidal delivery.

I. Anatomy of the Suprachoroidal Space
   A. OCT imaging of suprachoroidal space
   B. Methods to access the suprachoroidal space

II. Suprachoroidal Drug Delivery
   A. Suprachoroidal steroid for macular edema
   B. Suprachoroidal anti-VEGF therapies for neovascular diseases

III. Suprachoroidal Gene Delivery
   A. Suprachoroidal adeno-associated viral injections(AAV)
   B. Host immune responses to suprachoroidal AAV

References

1. Yiu G, Pecen P, Sarin N, et al. Characterization of the choroid-scleral junction and suprachoroidal layer in healthy individuals on enhanced-depth imaging optical coherence tomography. *JAMA Ophthalmol*. 2014; 132(2):174-181.
2. Emami-Naeini P, Yiu G. Medical and surgical applications for the suprachoroidal space. *Int Ophthalmol Clin*. 2019; 59(1):195-207.
3. Moisseiev E, Loewenstein A, Yiu G. The suprachoroidal space: from potential space to a space with potential. *Clin Ophthalmol*. 2016; 10:173-178.
4. Yeh S, Khurana RN, Shah M, et al. Efficacy and safety of suprachoroidal CLS-TA for macular edema secondary to noninfectious uveitis: Phase 3 randomized trial. *Ophthalmology* 2020; 127(7):948-955.
5. Campochiaro PA, Wykoff CC, Brown DM, et al. Suprachoroidal triamcinolone acetonide for retinal vein occlusion: results of the Tanzanite study. *Ophthalmol Retina*. 2018; 2(4):320-328.
6. Barakat MR, Wykoff CC, Gonzalez V, et al. Suprachoroidal CLS-TA plus intravitreal aflibercept for diabetic macular edema: a randomized, double-masked, parallel-design, controlled study. *Ophthalmol Retina*. 2021; 5(1):60-70.
7. Yiu G, Chung SH, Mollhoff IN, et al. Suprachoroidal and subretinal injections of AAV using transscleral microneedles for retinal gene delivery in nonhuman primates. *Mol Ther Methods Clin Dev*. 2020; 16:179-191.
8. Ding K, Shen J, Hafiz Z, et al. AAV8-vectored suprachoroidal gene transfer produces widespread ocular transgene expression. *J Clin Invest*. 2019; 130.
9. Shen J, Kim J, Tzeng SY, et al. Suprachoroidal gene transfer with nonviral nanoparticles. *Sci Adv*. 2020; 6(27).
10. Chung SH, Mollhoff IN, Mishra A, et al. Host immune responses after suprachoroidal delivery of AAV8 in nonhuman primate eyes. *Hum Gene Ther*. Epub ahead of print 2021 Apr 8. doi: 10.1089/hum.2020.281.

Real-World Outcomes of Voretigene Neparvovec (Luxturna) Subretinal Gene Therapy

Cagri G Besirli MD

Introduction

Voretigene neparvovec-rzyl was approved by the FDA in late 2017 as the first gene therapy targeted for treating patients with biallelic disease-causing variants in *RPE65*. Voretigene is an adeno-associated viral (AAV) vector-based gene therapy that preferentially delivers a functional copy of human *RPE65* cDNA to retinal pigment epithelium cells. The therapy is administered through subretinal injection, with transduction and transgenic gene expression typically occurring 2 to 4 weeks after subretinal injection. Following FDA approval, we treated and collected longitudinal data pre- and post-treatment of 23 eyes across 12 patients. We will be reporting real-world data on clinical outcomes of voretigene treatment from our center, as well as others that are published.

Study Design

A single-center retrospective chart review of patients treated with subretinal voretigene neparvovec for confirmed biallelic disease-causing variants in *RPE65*.

Results

Of the 9 eyes of 5 patients with baseline and 6-12 month follow-up data, full-field stimulus test (FST) improved for each eye after treatment. Mean follow-up FST significantly improved by 2.6 log-units ($P < .001$). Goldmann visual field also improved for each eye after surgery, although the degree of improvement was variable variable (see Figure 1).

There was no statistically significant change in visual acuity from baseline to last follow-up ($P = .23$), and visual acuity remained stable across follow-up visits (see Figure 2). There was no statistically significant change in CST from baseline to last follow-up ($P = .19$). There was a slight decrease in mean CST from baseline to 1 month post-treatment, and from 1 month to 2 months post-treatment, with stable mean CST after month 2, but this change was not statistically significant (see Figure 3).

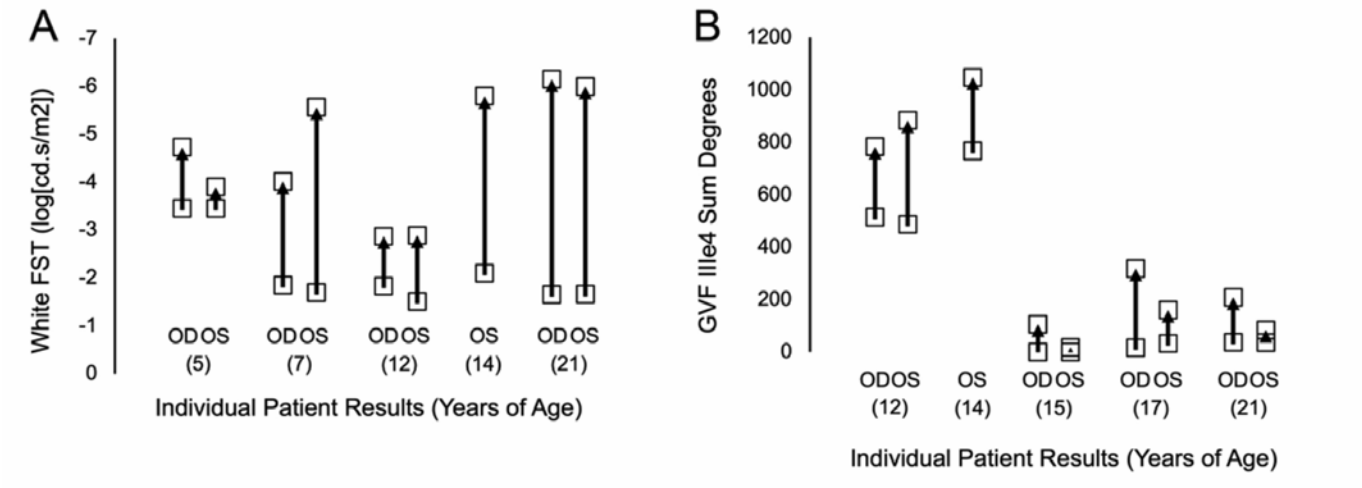


Figure 1

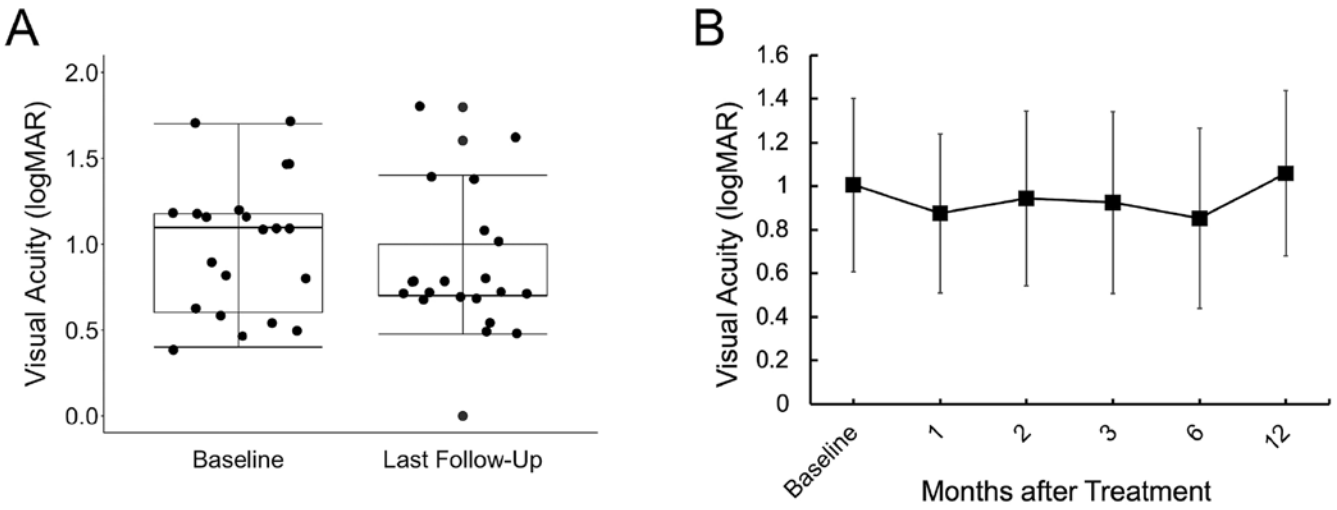


Figure 2

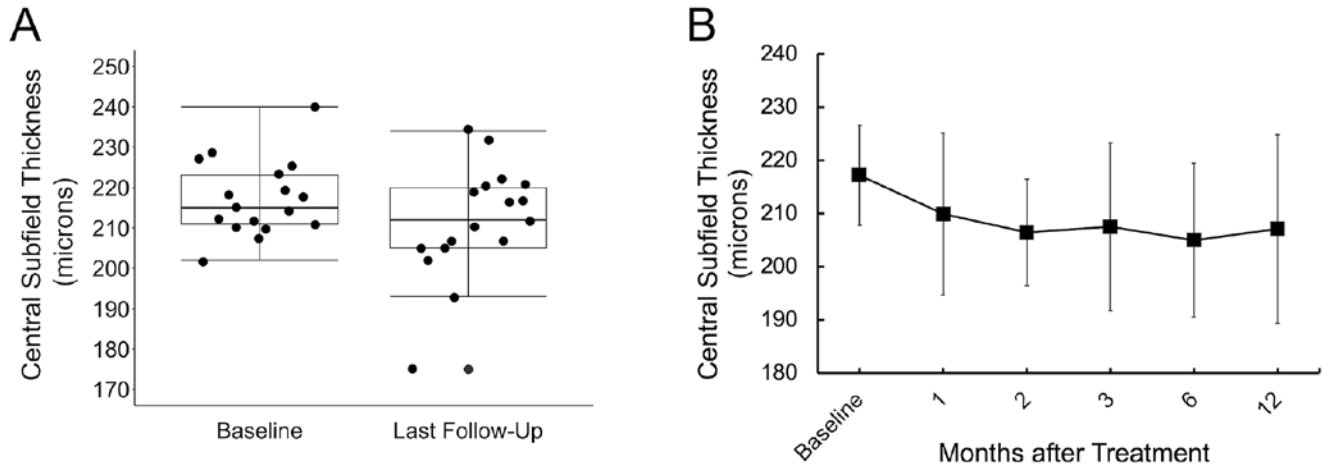


Figure 3

Conclusion

Our results are consistent with clinical trial data, demonstrating safe and effective treatment of patients with biallelic *RPE65* disease-causing variants beyond 6-12 months follow-up.

Selected Readings

1. Russell S, Bennett J, Wellman JA, et al. Efficacy and safety of voretigene neparvovec (AAV2-hRPE65v2) in patients with RPE65-mediated inherited retinal dystrophy: a randomized, controlled, open-label, Phase 3 trial. *Lancet* 2017; 390(10097):849-860.
2. Maguire AM, Russell S, Wellman JA, et al. Efficacy, safety, and durability of voretigene neparvovec-rzyl in RPE65 mutation-associated inherited retinal dystrophy: results of Phase 1 and 3 trials. *Ophthalmology* 2019; 126(9):1273-1285.
3. Kumaran N, Moore AT, Weleber RG, Michaelides M. Leber congenital amaurosis/early-onset severe retinal dystrophy: clinical features, molecular genetics and therapeutic interventions. *Br J Ophthalmol.* 2017; 101(9):1147-1154.

OpRegen Trial: Phase 1/2a Dose Escalation Study of Human Embryonic Stem Cell–Derived Retinal Pigment Epithelium Cells Transplanted Subretinally in Patients With Advanced AMD

NCT02286089: Interim Results and Further Insights From Imaging Analyses

Michael S Ip MD

Introduction

AMD is one of the leading causes of blindness in older adults living in the developed world, and the prevalence is expected to increase as the proportion of elderly in the general population grows larger.[1] Risk factors include both environmental and genetic factors, with older age identified as the major risk factor. There is an ~3-fold increase in the prevalence of the disease above the age of 65 years, and >25% of people older than 75 years suffer from advanced AMD, with loss of central vision due to either the neovascular (wet) form of AMD or the advanced dry form, with geographic atrophy (GA) that involves the fovea.[1-4] The pathogenesis of the disease involves abnormalities in 4 functionally interrelated tissues: retinal pigment epithelium (RPE), Bruch membrane, choriocapillaris, and photoreceptors. However, impairment of RPE cell function is an early and crucial event in the molecular pathways leading to clinically relevant AMD changes.[4] Recent publications have noted how rapid and severe the progression of GA can be in patients once diagnosed, and the disease represents an area of significant unmet medical need.[5-6]

Background

The cell-based product tested in this clinical study is composed of allogeneic RPE cells (OpRegen) originally derived from human embryonic stem cells (hESC) using a process of directed differentiation, under current good manufacturing practice (cGMP) conditions.[7-8] The hESC line was ethically approved for inclusion in the NIH Registry, though it is important to note that no other sources are required for any future applications. OpRegen cells were implanted as a cell suspension to the subretinal space of patients with dry AMD and GA in either ophthalmic Balanced Salt Solution Plus (BSS Plus) or Cyrostor 5 using either pars plana vitrectomy (PPV) and retinotomy, or via access through the suprachoroidal space using the Gyroscope Therapeutics Orbit Subretinal Delivery System (SDS). The working hypothesis and long-term goal in future studies is to establish that "young and healthy" allogeneic RPE cells, when transplanted early enough in the course of disease, will be able to support/replace host RPE cells that are dysfunctional/degenerating in patients with AMD, thus allowing attenuation of photoreceptor loss with better preservation of vision. This current Phase 1/2a trial is primarily designed to establish safety and tolerability, but the ability of the transplanted cells to survive and induce evidence of potential clinical benefit is also being assessed. We report interim safety and imaging data from all patients in the fully enrolled study ($N = 24$).

Methods

The process of preclinical development of the RPE cell preparation has been previously published.[7-8] The study was an open-label, dose escalation, international, multicenter Phase 1/2a trial (NCT02286089). Subretinal transplantation of 50-200k OpRegen cells in suspension to the worse vision eye used either PPV and retinotomy or the Orbit SDS. Short course, perioperative systemic immunosuppression was used. Endpoints include systemic and ocular safety and retinal structure and function.

Results

Patients (VA <20/200) in Cohorts 1-3 are in long-term follow-up (10/12; 2-5 years) or withdrawn (2/12). Twelve better seeing patients (<20/64 to >20/250) in Cohort 4 completed dosing in November 2020 (7 PPV:5 SDS). OpRegen has been well tolerated to date, with no unexpected adverse events (AEs). Using PPV, the most common ocular AEs were epiretinal membranes (ERM), in 15/17 eyes (88%), mostly mild to moderate; 3 (18%) severe ERM, requiring surgical peeling, all of which were successful. Two PPV-treated patients (2/17;12%) developed retinal detachments, 1 of which was successfully treated, and VA is now better than baseline. The other case was not followed long enough to determine success of the repair, as the patient withdrew due to unrelated stage 4 lung adenocarcinoma. In patients receiving OpRegen via the Orbit SDS, all AEs have been mild and included 1 asymptomatic extramacular type 2 CNV, successfully treated with a single anti-VEGF injection. Two additional cases of CNV have required repeated injections of an anti-VEGF but appear stable and VA exceeds baseline values. Improvement or maintenance of baseline VA (–6 to +19 letters) has been noted in 10/12 Cohort 4 patients (83%), which has been maintained from 6 months to ~3 years, while fellow eyes have decreased in 10/12 (83%) as of this submission. Treatment effects, including alterations in drusen appearance, subretinal pigmentation, and hyper-reflective areas, suggest persistence of transplanted OpRegen. Three patients have potential signs of retinal restoration and reduction in GA area based on OCT analyses of the periphery of the GA. Outer retinal layer restoration was evidenced by the presence of new areas of RPE monolayer with overlying ellipsoid zone, external limiting membrane, and outer nuclear layer, which were not present at the time of baseline assessment. These findings suggest integration of the new RPE cells with functional photoreceptors in areas that previously showed no presence of any of these cells. These patients continue to be followed. Additional image analyses by the team at the Doheny Eye Institute have observed statistically

significant differences between treated and fellow eyes at 1-year post-treatment as compared with baseline.

Conclusions

These data from advanced atrophic AMD patients represent interim observations of the ongoing study. Subretinal transplantation of OpRegen cells appears well tolerated. No unexpected ocular AEs have been observed, and most AEs have been mild in severity (87%). The most frequent AE was new or worsening ERMs, most of which were mild to moderate in severity, though 3 did require surgical peeling. Subretinal pigmentation that correlates with irregular subretinal hyper-reflectance on OCT is evident in most patients, suggesting the presence of cells in the subretinal space, which has remained stable for >5 years in some patients. Though it is not definitively known at this time whether these changes represent engraftment and survival of the transplanted cells, or possibly a reaction to the transplantation, immunohistochemical data from the preclinical in vivo pig experiments supports the former. Imaging findings suggest presence of transplanted cells in the subretinal space, and encouraging structural and clinical changes observed in some patients are being followed.

We continue to closely follow the outer retinal changes noted on OCT in patients where the surgical bleb of OpRegen cell suspension covered the area of atrophy, particularly in the areas of transition on the periphery of the lesions. VA has improved, or remained stable, in 10/12 treated eyes of Cohort 4 patients, ranging from 6 months to ~3 years post-transplant. We believe that transplantation of allogeneic RPE cells may represent a potential therapeutic option for dry AMD patients and are enthusiastic about the structural changes observed to date, though additional follow-up is ongoing.

References

1. Khurana R. What you should know about macular degeneration. Jan. 11, 2021. American Academy of Ophthalmology EyeSmart website. www.aao.org/eye-health/tips-prevention/six-things-about-amd.
2. Eye disease statistics. February 2014. American Academy of Ophthalmology ONE® Network website. www.aao.org/clinical-statement/eye-disease-statistics-2.
3. Wong WL, Su X, Cheung CMG, Klein R, Cheng CY, Wong TY. Global prevalence of age-related macular degeneration and disease burden projection for 2020 and 2040: a systematic review and meta-analysis. *Lancet Glob Health*. 2014; 2:e106-116.
4. Hadziahmetovic M, Malek G. Age-related macular degeneration revisited: from pathology and cellular stress to potential therapies. *Front Cell Dev Biol*. 2021; 8:612812.
5. Chakravarthy U, Bailey CC, Johnston RL, et al. Characterizing disease burden and progression of geographic atrophy secondary to age-related macular degeneration. *Ophthalmology* 2018; 125(6):842-849.
6. Holekamp N, Wykoff CC, Schmitz-Valckenberg S, et al. Natural history of geographic atrophy secondary to age-related macular degeneration: results from the prospective Proxima A and B clinical trials. *Ophthalmology* 2020; 127(6):769-783.
7. Idelson I, Obolensky A, Ben-Shushan E, et al. Directed differentiation of human embryonic stem cells into functional retinal pigment epithelium cells. *Cell Stem Cell*. 2009; 5(4):396-408.
8. McGill TJ, Bohana-Kashtan O, Stoddard JW, et al. Long-term efficacy of GMP grade xeno-free hESC-derived RPE cells following transplantation. *Trans Vis Sci Tech*. 2017; 6(3):17.

Intravitreal Human Retinal Progenitor Cells for the Treatment of Retinitis Pigmentosa

Baruch D Kuppermann MD

Background

Retinitis pigmentosa (RP) is an incurable eye disease that begins destroying retinal cells following birth, ultimately leading to blindness. RP affects approximately 2 million people worldwide and is considered a rare disease. Other than voretigene neparvovec-rzyl, a gene therapy indicated for the treatment of the RPE65 mutation, which represents <1% of all RP patients, there is no effective treatment for RP; once photoreceptors die, they do not regenerate. The rate of deterioration of vision varies, with most people with RP are legally blind by age 40.

When used therapeutically, retinal progenitor cells (RPC) show promise as a therapeutic strategy for RP as they secrete neurotrophic factors that promote retinal photoreceptor cell survival and function. Preclinical studies conducted by jCyte demonstrated that an injection of their RPC therapy, jCell, into the eye induces a paracrine mechanism of effect that results in significant slowing of host photoreceptor loss and reactivation of dormant and inactive, but still structurally viable, retinal cells.

jCyte has focused on evaluating jCell, which is administered via intravitreal injection, in a Phase 2b study that enrolled a broad spectrum of RP subjects with impacted visual acuity (20/80-20/800). The main purpose of the study was to better understand (1) the optimal jCell intravitreal dose, (2) the most clinically meaningful endpoints for measuring visual function and functional vision in this heterogenous population, and (3) the RP subpopulation who would likely benefit most from a single jCell intravitreal treatment during a 12-month pivotal trial. Due to the nascency of clinical study within the field and an absence of large clinical trials conducted within a representative subset of all RP subjects, broad inclusion criteria were applied for this Phase 2b clinical trial, the largest ever for a locally administered investigative treatment. As a result, many of the subjects enrolled into the trial were severely impaired with little remaining visual field, or only peripheral islands of vision. Many patients also had a large imbalance in function between eyes, with a strong dependence on their eye that had better remaining vision. Lastly, many of the patients had little to no remaining ellipsoid zone (EZ) and central foveal thickness (CFT), both of which serve as potential structural surrogates for disease severity in RP.

jCyte Study Design

The trial was conducted to evaluate jCell for the treatment of RP in a broad spectrum of patients. Patients with RP and BCVA between 20/80 and 20/800 were randomized to treatment vs. sham. Treatment consisted of $3.0x10^6$ or $6.0x10^6$ RPC via a single intravitreal injection. The primary efficacy endpoint was mean change in BCVA at Month 12. Secondary endpoints included the low luminance mobility test (LLMT), contrast sensitivity (CS), kinetic visual fields (VF), and a vision function questionnaire (VFQ). In a post hoc analysis aimed at evaluating the treatment effect of jCell within a reliable and measurable population, the primary and secondary endpoints were assessed in a target subgroup of patients meeting the following criteria: (1) study eye with a minimum visual field diameter as well as reliable fixation (steady central fixation and ≥12° central diameter) and (2) study eye did not have significantly worse BCVA than the fellow eye (≤15 letters).

To support the identification of baseline anatomical markers predictive of efficacy in the more measurable and reliable target subgroup, the Cleveland Clinic Cole Eye Institute analyzed readable spectral domain OCT (SD-OCT) volumetric data, in which frame-by-frame macular cube scans were processed using automated segmentation, followed by EZ mapping with manual correction for segmentation errors by masked graders. Measures of mean foveal thickness within the subfield or mid-subfield, as well as EZ–retinal pigment epithelium subfield or mid-subfield volume and thickness, were generated, and correlational analysis was performed between each OCT parameter and change in each of the Phase 2b trial endpoints from baseline to 12 months.

jCyte Results

A total of 84 patients were randomized, and 37 met the criteria for the post hoc analysis of the target subgroup. Results for the target subgroup are shown below:

- Mean changes in BCVA from baseline to Month 12 were +1.85, −0.15, and +16.27 letters in the sham arm (n = 13), $3.0x10^6$ RPC arm (n = 13), and $6.0x10^6$ RPC arm (n = 11), respectively (P = .003 for $6.0x10^6$ RPC vs. sham).
- Improvements in the $6.0x10^6$ RPC target subgroup compared to sham were also observed in all secondary endpoints.

For the SD-OCT analysis performed by the Cleveland Clinic Cole Eye Institute, there were 29 readable scans from the target subgroup, with the strongest relationship demonstrated in mean central foveal thickness (CFT):

- Strong, statistically significant correlations were shown in the $6.0x10^6$ RPC arm (n = 10) between mean CFT and change in each of the Phase 2b trial endpoints from baseline to 12 months, with greater CFT values corresponding to greater improvements in each endpoint
  - R = 0.88 (BCVA), 0.78 (VF), 0.79 (CS), 0.72 (LLMT), and 0.82 (VFQ)
  - P < .05 for BCVA, VF, CS, LLMT, and VFQ
- Moderate to strong correlations were also seen in the same group between change in all trial endpoints and mid-subfield mean EZ thickness.
- The sham (n = 10) and $3.0x10^6$ RPC (n = 9) arms did not demonstrate any significant relationships.

Adverse events were generally minor and transient; there was 1 serious adverse event in the $3.0x10^6$ RPC arm of grade-3 ocular hypertension that resolved with treatment.

jCyte Summary

Intravitreal injection of RPC is a novel approach for treatment of RP that appears to be effective independent of the genetic subtype. This Phase 2b study demonstrates encouraging biological activity and a good safety profile and provides valuable information regarding the optimal jCell dose, the most clinically meaningful trial endpoints, and the baseline structural characteristics of the patients likely to have the largest clinical response from a single jCell treatment during a 12-month study period. These data warrant progression to a Phase 3 trial utilizing a higher dose, such as $6.0x10^6$ RPC, in a RP patient population that has less variability (eg, having the ability to fixate reliably during testing), and one that is in an earlier, less severe disease stage as represented by having a certain minimum mean CFT or EZ thickness.

Summary: Intravitreal RPC for RP

RPCs are a class of stem cells that have undergone lineage restriction to become retinal precursor cells. They are being evaluated by jCyte in the treatment of RP via intravitreal injection, and data collected to date suggest that certain baseline structural markers, such as CFT and EZ, may serve as important predictors of response. Available results show promising efficacy and good safety, and additional data will be shared in the AAO 2021 Subspecialty Day presentation.

Selected Readings

1. Klassen H, Imfeld KL, Ray J, et al. The immunological properties of adult hippocampal progenitor cells. *Vision Res*. 2003; 43:947-956.
2. Klassen HJ, Ng TF, Kurimoto Y, et al. Multipotent retinal progenitors express developmental markers, differentiate into retinal neurons, and preserve light-mediated behavior. *Invest Ophthalmol Vis Sci*. 2004; 45(11):4167-4173.
3. Klassen H, Zaiaeian B, Kirov II, Young MJ, Schwartz PH. Isolation of retinal progenitor cells from post-mortem human tissue and comparison with autologous brain progenitors. *J Neurosci Res*. 2004; 77(3):334-343.
4. MacLaren RE, Pearson RA, MacNeil A, et al. Retinal repair by transplantation of photoreceptor precursors. *Nature* 2006; 444(7116):203-207.
5. Young MJ, Ray J, Whiteley SJ, Klassen H, Gage FH. Neuronal differentiation and morphological integration of hippocampal progenitor cell transplanted to the retina of immature and mature dystrophic rats. *Mol Cell Neurosci*. 2000; 16:197-205.
6. Srivastava S, Kaiser PK, Kammer R, et al. Predictive relationship of OCT characteristics for efficacy in an intravitreal injection of allogeneic human retinal progenitor cells (hRPC) for the treatment of retinitis pigmentosa. *Invest Ophthalmol Vis Sci*. 2021; 62:3233.

OCT Risk Factors for Late AMD: Implications for Clinical Practice

Srinivas R Sadda MD

I. Color Fundus Risk Factors for Progression to late AMD
   A. Drusen area
   B. Large drusen
   C. Depigmentation
   D. Hyperpigmentation

II. AREDS 9-Step Scale
   A. Based on estimating features on color photos using standard circles/grid
   B. Correlates with risk for progression to late AMD at 5 years
   C. Useful for clinical trials and reading centers
   D. Not practical for clinical practice

III. Simplified AREDS 5-Step (0-4 Point) Scale
   A. Also based on color photos or fundus exam
   B. Only requires identifying presence of large drusen or pigment changes in each eye
   C. Each of the 2 features in each eye earns 1 point, or a maximum total of 4, for the 2 eyes combined.
   D. Also correlates with risk for progression to late AMD at 5 years
      1. 0 point: 0.5%
      2. 1 point: 3%
      3. 2 points: 12%
      4. 3 points: 25%
      5. 4 points: 50%
   E. Clinically useful, but we are shifting from color photos to OCT.

IV. OCT Risk Factors for Development of Late AMD
   A. Intraretinal hyperreflective foci (pigment migration)
   B. Hyporeflective cores in drusen (calcific nodules)
   C. Subretinal drusenoid deposits (reticular pseudodrusen)
   D. High central drusen volume (≥0.03 mm^3 within the central 3 mm)
   E. Nonexudative macular neovascularization

V. Developing a Risk Scoring System Based on OCT Risk Factors

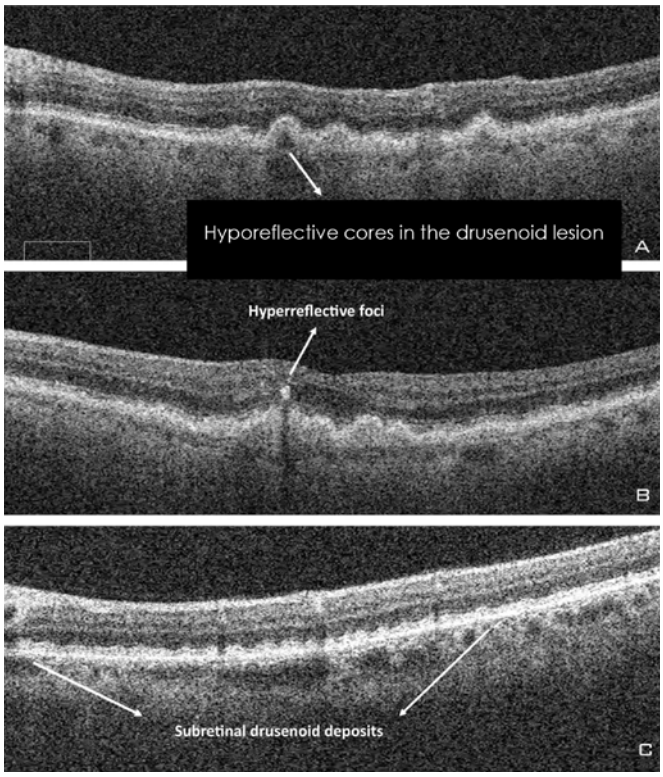


Figure 1

Table 1

Risk Factors	Scores, OD	Scores, OS
Hyporeflective drusen cores	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, hyper-reflective foci; SDD, subretinal drusenoid deposits.

Max score = 8 points. Divide by 2 to create 4-point scale similar to AREDS simple scale.

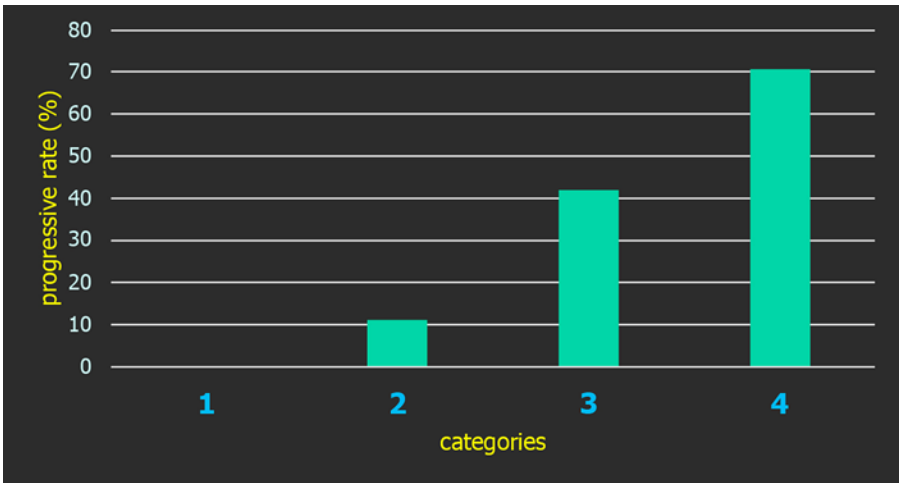


Figure 2

VI. Risk for Progression to late AMD and OCT Simple Scale (Lei et al, *Graefes* 2017)

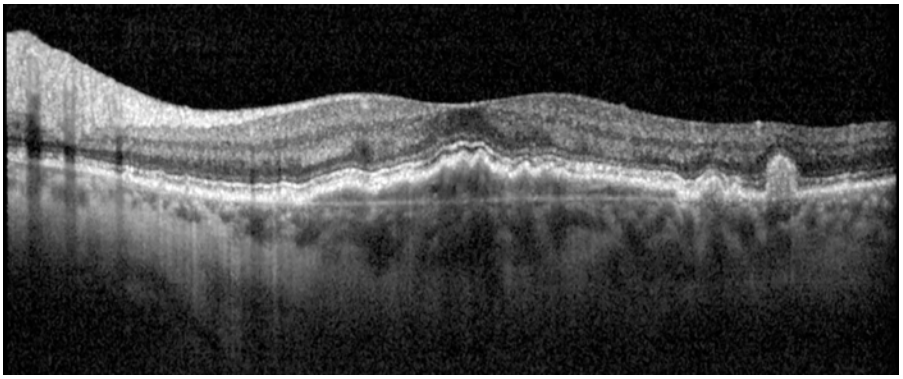


Figure 3

A. Nonexudative macular neovascularization is a new risk factor – increases risk of conversion to exudation.

B. OCT risk factors may be used for prognostication and for determining monitoring intervals for patients with intermediate AMD.

Morphologic Features at Conversion From Nonexudative to Exudative AMD

Usha Chakravarthy MBBS PhD, Tunde Peto MD PhD, and Savita Madhusudhan MBBS FRCOphth

EDNA was a multicenter, prospective, cohort diagnostic accuracy study testing 5 index tests in a routine clinical monitoring setting. At recruitment (baseline), participants had to have a confirmed diagnosis of nonexudative AMD (nAMD) of recent onset in the first presenting eye and no active nAMD in the second eye (designated the EDNA study eye). An eligibility criterion was treatment with an anti-VEGF to the first presenting eye as it was considered that such patients would have a high frequency of attendance over subsequent years, allowing the collection of and extraction of pragmatic routine clinical data during follow-up. After enrollment, both eyes of participants were monitored in each clinical site for up to 3 years or until onset of nAMD in the study eye.

Clinical sites monitored and reviewed patient attendance records and collected data on index tests: self-report of progressive worsening of vision, distortion on Amsler, drop in visual acuity, detection by fundus examination of signs of nAMD, and signs of exudation in the macula on OCT with all tests pertaining to the EDNA study eye. Clinical care teams were instructed to request a fundus fluorescein angiography FFA in the event that any of the index tests were positive (a trigger) for nAMD. In the absence of a trigger, planned study visits were undertaken at 18 months or at study exit, which occurred after a minimum of 30 months of follow-up, at which time a detailed clinical assessment and retinal imaging that included FFA was performed. Of the 552 participants enrolled into EDNA, 145 developed nAMD in the EDNA study eye, of whom 120 had an FFA at the time of detection. In 119 of these, the FFA was also read by the reading center. In this analysis we compare the characteristics of nAMD lesions at detection in the 119 (early lesions) to those of matched fellow eyes at initial presentation (ie, enrollment).

On comparing the proportions with type 1, 2, and 3 lesions between matched fellow eyes and EDNA study eyes, these were found similar. On average, the area dimensions of the total lesion and active neovascular complex were markedly smaller in EDNA study eyes (less than half the size) compared to matched fellow eyes. Within the study eye population, type 1 were larger than type 2 or retinal angiomatous proliferation (RAP) lesions. Compared to matched fellow eyes, lesions were more likely to be extrafoveal or juxtafoveal in the EDNA study eye. In type 1 lesions, 50% were subfoveal at detection of nAMD in the EDNA study eye compared to over 80% that were subfoveal in the fellow eye. In type 2 lesions, fewer than 10% were subfoveal in the EDNA study eye compared to 50% subfoveal location in corresponding fellow eyes. Of lesions classified as RAP, none were subfoveal in the EDNA study eye at conversion to exudative nAMD, with these lesions equally distributed between extra- and juxtafoveal locations. In study eyes, fibrosis was rare when the nAMD lesion was detected. Features of atrophy in the outer retina was observed at the same frequency as in matched fellow eyes.

The characteristics of the EDNA study eye—of smaller lesions with mainly extrafoveal location—are in accord with the better function in study eyes even though there had been conversion to nAMD. Notably, mean visual acuity in the study eye of the 119 participants at detection of conversion to nAMD was 78 letters. Interestingly, these data explain the low sensitivity of self-reported reduction in visual function, which was 5% despite the better functional status of the study eye at enrollment. The average visual acuity of corresponding fellow eyes at initial presentation was 54 letters, a difference of approximately 4 ETDRS lines compared to the early detection group. As 15 letters (3 ETDRS lines) equates to a halving or doubling of the visual angle on the ETDRS chart, the difference shows the importance of early detection and the benefit in terms of avoiding a considerable deficit of visual acuity caused by delayed detection of nAMD in first-presenting eyes.

Ten-Year Follow-up Data From the AREDS2 Study

Emily Y Chew MD and the Age-Related Eye Disease Study 2 (AREDS2)

Purpose

To assess the long-term effects of adding lutein/zeaxanthin and omega-3 fatty acids to the Age-Related Eye Disease Study (AREDS) supplements on age-related macular degeneration (AMD) progression and adverse side effects.

Methods

The AREDS2 clinical trial randomly assigned participants with bilateral intermediate AMD or late AMD in 1 eye to lutein/zeaxanthin and/or omega-3 fatty acids or placebo. Secondary randomization also evaluated varying doses of beta-carotene (0 vs. 15 mg) and zinc (25 vs. 80 mg). At the end of the 5-year clinical trial, a follow-up study was conducted with 6-monthly telephone calls to the surviving AREDS2 participants from the central coordinating center to collect outcome data and adverse events for safety monitoring for an additional 5 years. Medical records were obtained from treating physicians to validate any self-reported diagnosis or treatment of late AMD and cataract and side effects. AREDS2 supplements with lutein/zeaxanthin, vitamin C and E, and zinc plus copper were provided to all participants during this additional follow-up. Repeated measures logistic regression was used in the primary analyses.

Results

6360 study eyes (3887 participants) were analyzed, and 3047 (48%) progressed to late AMD. The main effects of lutein/zeaxanthin vs. no lutein-zeaxanthin and of omega-3 fatty acids vs. no omega-3 fatty acids resulted in hazard ratios (HRs) of 0.91 (95% CI, 0.89 to 0.99; $P = .03$) and 1.00 (95% CI, 0.92 to 1.09; $P = .91$), respectively. When the lutein/zeaxanthin main effect analysis was restricted to those randomized secondarily to beta-carotene, the HR was 0.80 (95% CI, 0.69 to 0.92; $P = .003$). On direct analysis of lutein/zeaxanthin vs. beta-carotene, the HR was 0.85 (95% CI, 0.74 to 0.98; $P = .03$). For the comparisons of low vs. high zinc and no beta-carotene vs. beta-carotene, the HRs were 1.04 (95% CI, 0.94 to 1.14; $P = .48$) and 1.04 (95% CI, 0.93 to 1.15; $P = .50$), respectively. For those randomized to beta-carotene, the odds ratio (OR) of developing lung cancer was 1.82 (95% CI, 1.06 to 3.12; $P = .02$), while the OR for those randomized to lutein/zeaxanthin was 1.15 (95% CI, 0.79-1.66; $P = .46$).

Conclusions

The 10-year follow-on study replicated the findings of the randomized clinical trial at 5 years.[1,2] Lutein/zeaxanthin, when compared with beta-carotene, had an incremental beneficial effect on progression to late AMD. Beta-carotene doubled the risk of lung cancer, providing support for lutein/zeaxanthin as a replacement for beta-carotene in the AREDS2 supplements.

References

1. Age-Related Eye Disease Study 2 Research Group. Lutein + zeaxanthin and omega-3 fatty acids for age-related macular degeneration: the Age-Related Eye Disease Study 2 (AREDS2) randomized clinical trial. *JAMA*. 2013; 309(19):2005-1015.
2. Age-Related Eye Disease Study 2 (AREDS2) Research Group; Chew EY, Clemons TE, Sangiovanni JP, et al. Secondary analyses of the effects of lutein/zeaxanthin on age-related macular degeneration progression: AREDS2 report No. 3. *JAMA Ophthalmol*. 2014; 132(2):142-149.

Nascent Geographic Atrophy

What Is It, and Why Is It Important?

Robyn Guymer MBBS PhD

Introduction

The evaluation of potential interventions to delay the progression of AMD to its late complications remains a challenge, in part due to the lack of validated earlier clinical biomarkers and endpoints that would improve the feasibility of conducting early intervention trials. In eyes with the early stages of AMD, we have previously described features on OCT imaging that precede the development of geographic atrophy (GA) as determined on color fundus photography (CFP), and we termed these features "nascent geographic atrophy" (nGA).[1] We hypothesize that nGA provides a high-risk feature predicting progression to GA and could be an early endpoint for trials.

The features of nGA include the subsidence of the inner nuclear layer (INL) and outer plexiform layer (OPL) and/or the presence of a hyporeflective wedge-shaped band within the Henle fiber layer; both indicating a loss of the photoreceptor layer. We defined these specific features of nGA as we believe their presence greatly enriches a population that progresses to GA and provides a new earlier robust endpoint for early intervention trials.[3] Subsequently, the Classification of Atrophy (CAM) international consensus group have used the term "incomplete RPE (retinal pigment epithelial) and outer retinal atrophy" (iRORA) to encapsulate the early OCT findings that can be observed in each relevant OCT layer—the RPE, outer retina, and choroid—at the beginning of cell death or atrophy.[2] In the CAM definitions, iRORA closely resembles the original definition of nGA, and many cases of nGA satisfy the criteria for iRORA, but the reverse is not as often the case, as there are many cases of iRORA that do not have subsidence or the wedge and as such are not nGA as originally described. While in the CAM 4 paper we encouraged the use of the term "nGA" to be more broadly applicable to iRORA, there is still great value in being very precise when considering which OCT features are required to be present when determining risks of progression toward vision loss, reproducibility of grading each of the required features, and the robustness of the combined features to be an endpoint in a trial.

The aim of this study was to determine the risk of developing GA, as determined on CFP, in eyes with intermediate AMD that had already developed nGA.

Methods

We evaluated a prospective longitudinal observational study of 284 eyes from 142 participants with bilateral large drusen and without nGA or late AMD at baseline. OCT scans and CFPs were obtained at baseline and then at 6-monthly intervals for 36 months. OCTs and CFPs were graded for the presence of nGA and GA, respectively.

Main outcome measures

The time taken and number of nGA cases that developed GA

Results

The proportion of eyes progressing from first detection of nGA to GA was 23%, 38%, and 56% after 18, 24, and 30 months, respectively. In eyes that developed nGA, there was a marked increased risk of progression to GA compared to eyes that did not develop nGA (adjusted hazard ratio = 78.1; 95% CI = 13.6 to 448.0; $P < .001$). The development of nGA explained 91% of the variance in the time to develop GA.

Discussion

This study prospectively demonstrated that nGA—as it was originally defined with OPL/INL subsidence and/or a hyporeflective wedge-shaped band—was highly predictive of the development of CFP-defined GA in a cohort with bilateral large drusen. This very high hazard ratio does not necessarily translate to other atrophic features that might satisfy the definition of iRORA but not nGA, and further work is needed to determine the predictive value of iRORA for the development of GA. The inclusion of nGA as an outcome measure can substantially improve the feasibility of evaluating new interventions for the early stages of AMD. These results provide supportive evidence of the potential value of nGA as an endpoint for interventional trials.

Conclusion

This study prospectively demonstrated that nGA—defined as eyes with the OCT signs of subsidence of the INL and OPL and/or the presence of a hyporeflective wedge-shaped band—was a strong predictor for the development of GA, providing supportive evidence of the potential value of nGA as an endpoint in future intervention trials.

References

1. Wu Z, Luu CD, Ayton LN, et al. Optical coherence tomography defined changes preceding the development of drusen-associated atrophy in age-related macular degeneration. *Ophthalmology* 2014; 121(12):2415-2422.
2. Guymer RH, Rosenfeld PJ, Curcio CA, et al. Incomplete retinal pigment epithelial and outer retinal atrophy in age-related macular degeneration: Classification of Atrophy Meeting Report 4. *Ophthalmology* 2020; 127:394-409.
3. Guymer RH, McGuinness M, Hodgson LA, Luu CD, Wu Z. Nascent geographic atrophy as a surrogate endpoint in age-related macular degeneration. *Invest Ophthalmol Vis Sci*. 2019; 60:2214.

Is All Macular Atrophy the Same?

Giovanni Staurenghi MD

I. The Classification of Atrophy Meetings (CAM) program introduced a consensus terminology and criteria for defining atrophy based on OCT findings in the setting of AMD.

A. New terms were suggested, such as:

1. Complete retinal pigment epithelium and outer retina atrophy (c-RORA)
2. Incomplete retinal pigment epithelium and outer retina atrophy (i-RORA)
3. Complete outer retina atrophy (c-ORA)
4. Incomplete outer retina atrophy (i-ORA)

B. The same group suggested the imaging protocols to define the differences in macular atrophy. One of the new biomarkers identified with the new imaging modalities is subretinal drusenoid deposits (SDD), AKA "pseudodrusen" or "reticular pseudodrusen," referring to material that has accumulated between the RPE and photoreceptors and may extend into the outer retina.

C. Near infrared confocal imaging, confocal autofluorescence, and OCT are the best imaging modality used to identify SDD.

II. These lesions are common in different pathologies

A. AMD

B. Extensive macular atrophy with pseudodrusen-like appearance (EMAP)

C. Pseudoxanthoma elasticum

III. In EMAP, atrophy has same characteristics of macular atrophy secondary to AMD.

A. Severe form of geographic atrophy with predominant vertical axis and early foveal involvement

B. Contoured by a lattice of yellowish flat drusen until retinal midperiphery

C. Frequent peripheral paving stone lesions

D. Visual symptoms onset at 45-55 years of age

E. No evidence of genetic background

F. Suspicious regionality

IV. Previous publications suggested the importance of indocyanine green angiography and OCT angiography to differentiate late-onset Stargardt disease (LOSD) and AMD.

A. In LOSD there is absence of choriocapillaris and Sattler layers in the central part of the atrophy.

B. This characteristic is not visible in AMD due to the presence of some RPE cells remaining in the atrophic area.

Multicenter, Head-to-Head, Real-World Validation Study of 7 Automated AI Diabetic Retinopathy Screening Systems

Aaron Y Lee MD, Ryan T Yanagihara, Cecilia S Lee, Marian Blazes, Hoon C Jung, Yewlin E Chee, Michael D Gencarella, Harry Gee, April Y Maa, Glenn C Cockerham, Mary Lynch, and Edward J Boyko

The US FDA has approved 2 fully automated artificial intelligence (AI) algorithms for teleretinal diabetic retinopathy (DR) screening systems. Several others are under consideration while in clinical use in other countries, but their real-world performance has not been evaluated systematically. We compared the performance of 7 automated AI-based DR screening algorithms (including 1 FDA-approved algorithm) against human graders when analyzing real-world retinal imaging data from OphthAI, AirDoc, Eyenuk, Retina-AI Health, and Retmarker.

This was a multicenter, noninterventional device validation study evaluating a total of 311,604 retinal images from 23,724 veterans who presented for teleretinal DR screening at the Veterans Affairs (VA) Puget Sound Health Care System (HCS) or Atlanta VA HCS from 2006 to 2018. Five companies provided 7 algorithms, including 1 with FDA approval, that independently analyzed all scans, regardless of image quality. The sensitivity/specificity of each algorithm when classifying images as referable DR or not were compared with original VA teleretinal grades and a regraded arbitrated data set. Value per encounter was estimated.

Although high negative predictive values (82.72%-93.69%) were observed, sensitivities varied widely (50.98%-85.90%). Most algorithms performed no better than humans against the arbitrated data set, but 2 achieved higher sensitivities, and 1 yielded comparable sensitivity (80.47%, $P = .441$) and specificity (81.28%, $P = .195$). Notably, 1 had lower sensitivity (74.42%) for proliferative DR ($P = 9.77 \times 10–4$) than the VA teleretinal graders. Value per encounter varied, at \$15.14-\$18.06 for ophthalmologists and \$7.74-\$9.24 for optometrists.

The DR screening algorithms showed significant performance differences. These results argue for rigorous testing of all such algorithms on real-world data before clinical implementation.

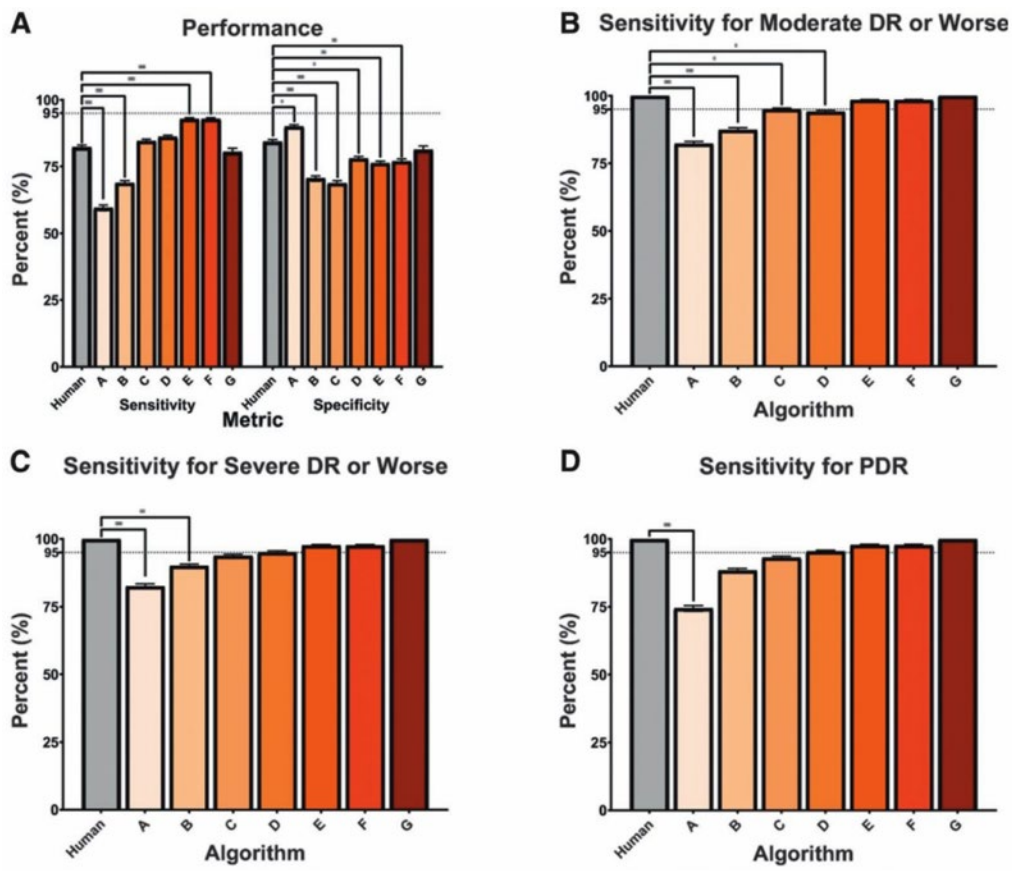


Figure 1. Relative performance of human grader compared with AI algorithms. The relative performance of the VA teleretinal grader (Human) and algorithms A–G in screening for referable DR using the arbitrated data set at different thresholds of DR. (A) Sensitivity and specificity of each algorithm compared with a human grader with 95% CI bars against a subset of double-masked arbitrated grades in screening for referable DR in images with mild nonproliferative diabetic retinopathy (NPDR) or worse and ungradable image quality. (B-D) Only gradable images were used. The VA teleretinal grader is compared with the AI sensitivities, with 95% CIs, at different thresholds of disease, including moderate NPDR or worse (B), severe NPDR or worse (C), and PDR (D). *$P \leq .05$, **$P \leq .001$, ***$P \leq .0001$.

Prediction of Systemic Diseases From Eye Images Using AI and Deep Learning

Tien Y Wong MBBS

Introduction

The eye is the sole organ in the body that allows for the direct observation and imaging of the neurological and vascular system. In recent years, researchers have harnessed the noninvasive nature of color fundus photographs (CFPs) to examine changes in the retina as a possible marker of systemic disease risk. Building on large-scale epidemiological studies that have reported relationships of retinal features such as retinal vascular caliber with systemic diseases, the application of artificial intelligence (AI) technology, specifically in deep learning (DL), on CFPs is advancing new research that focuses on retina-systemic disease relationships.

In this new field, current studies fall into 2 basic groups (Figure 1):

1. Cross-sectional studies that use AI-DL technology on CFPs to detect or estimate systemic risk factors (eg, age, blood pressure, smoking) or other biomarkers (eg, coronary artery calcium)
2. Longitudinal studies that use AI-DL technology on CFPs to predict the incidence or risk of systemic disease (eg, cardiovascular disease [CVD] event or mortality).

Prediction of Demographic, Lifestyle Factors, and Body Composition

AI-DL has been used on CFP for the prediction of demographic and lifestyle factors, specifically, age, gender, smoking status, and body composition. Most studies have investigated age as a predictable variable from CFP via AI-DL. Chronological age is the most reliable at portraying growth milestones accurately,[1] and the retina is considered the "window" to the whole body. Therefore, predicting age from CFP via AI-DL could provide valuable information about the status of a target organ and/or the body.[2] In addition to age as a predictor, the ability to identify sex with high confidence from CFP via AI-DL has been demonstrated in similar studies. For example, Rim et al showed fair results in their external multiethnic test sets for both age (coefficient of determination, R^2 = 0.36-0.63) and sex (area under a curve [AUC] = 0.80-0.91) predictions, demonstrating reasonable generalizability on predicting sex and age from CFPs.[3]

In terms of lifestyle factors, smoking status is commonly assessed because of the direct link between CVD and smoking habits. A number of studies examined the use of CFP to predict smoking status, with reasonable results (AUC = 0.71-0.86).[4-6]

BMI has also been predicted from CFP via AI-DL, although there is great variability in mean absolute error (MAE) with a low generalizability across the ethnic groups.[3,4] Recently, Rim et al developed an AI-DL model that enabled the quantification of muscle mass from CFP.[3] The MAE (6.09 kg) was high, and the coefficient of determination (R^2 = 0.33) was low in the external testing set, reiterating the need for further validation studies before assessing whether CFP could be used as an alternative screening tool for sarcopenia.

Prediction of Anemia

AI-DL has been shown to predict anemia and related biomarkers, including hemoglobin, hematocrit, and red blood cells, in different studies.[3,6,7] Anemia was predictable using an AI-DL model developed by Mitani et al, with a relatively good AUC of 0.88 using a combined model of systemic risk factors and CFPs.[7] However, Rim et al tested the use of AI-DL to predict a range of hematologic factors in external datasets and found limited generalizability across ethnic groups.[3]

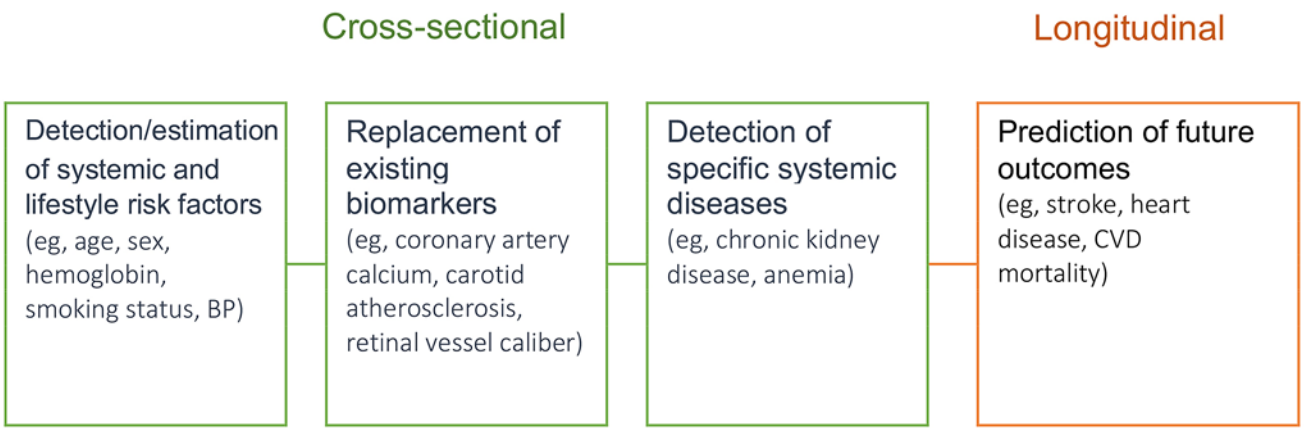


Figure 1. Framework for artificial intelligence to evaluate systemic disease via the eye.

Prediction of Kidney Disease

Few studies have explored the prediction of chronic kidney disease (CKD) from CFP. Of note, Sabanayagam et al[8] predicted CKD (AUC = 0.73) with modest generalizability, and a separate AI-DL system developed by Kang et al[9] achieved an AUC of 0.81, although no external validation was conducted. In particular, the performance of the model developed by Sabanayagam et al was generally stable (AUC > 0.9 for all models) across the different models (ie, CFP, risk factors, combined) that were trained, suggesting that risk factor information was not required for CKD risk assessment in patients.

Prediction of Retinal Vessel Caliber

There is strong evidence from epidemiological studies that changes in the retinal vasculature mirror systemic microcirculation changes. However, the process for assessing retinal vascular changes is time-consuming and requires professional training, which has limited the expansion and wider application of these traditional methods. To address these challenges, AI-DL was applied to measure retinal vessel diameter (SIVA-DLS). The SIVA-DLS study reported high intraclass correlation coefficients (0.82-0.95) between the SIVA-DLS and validated human measurements.[10] The team found that a narrow central retinal arteriolar equivalent measured by SIVA-DLS was associated with incident CVD and all-cause mortality in 2 prospective cohorts.

Prediction of Cardiovascular Diseases

There are a limited number of prospective studies on the relationship between AI-DL technology applied to CFP on risk of CVDs and CVD mortality. Poplin et al predicted CVD risk factors from CFP via AI-DL and thereafter used the results to predict CVD events over 5 years in the UK Biobank.[4] Lim et al evaluated the potential of an AI-DL model as an ischemic stroke risk assessment from CFP, and this resulted in a varying AUC of 0.685-0.994 for 6 different datasets.[11]

Coronary artery calcium (CAC) is a preclinical marker of atherosclerosis and is strongly associated with risk of clinical CVD. Recently, Son et al created an AI-DL model to predict abnormal CAC from CFP, both unilaterally and bilaterally, and the performance (AUC = 0.823-0.832) was promising.[12] Rim et al also developed an AI-DL model to predict CAC from CFP (termed "RetiCAC") using a large Korean dataset, with external validation of the estimated CAC (Reti-CAC) in predicting CVD events in the UK Biobank.[13]

Chang et al developed an AI-DL model to predict carotid artery atherosclerosis measured by carotid intima media thickness (IMT), and the model was able to predict ultrasonographically confirmed carotid artery atherosclerosis with an AUC of 0.713.[14] The study demonstrated that the retinal biomarker was significantly associated with an increased risk, represented by hazard ratio, for CVD mortality after adjusting for the Framingham risk score.

Conclusion

The eye provides an opportunity to predict systemic disease factors using CFP.[15] Various studies have shown this potential, but further efforts are needed. To date, prospective studies and evidence in real-world settings are insufficient, and therefore the clinical application of AI-DL models using CFP to predict systemic diseases is limited.

References

1. Kim YD, Noh KJ, Byun SJ, et al. Effects of hypertension, diabetes, and smoking on age and sex prediction from retinal fundus images. *Sci Rep.* 2020; 10(1):4623.
2. Zhu ZT, Shi DL, Peng GK, et al. Retinal age as a predictive biomarker for mortality risk. medRxiv, Dec. 30 2020. doi: https://doi.org/10.1101/2020.12.24.20248817.
3. Rim TH, Lee G, Kim Y, et al. Prediction of systemic biomarkers from retinal photographs: development and validation of deep-learning algorithms. *Lancet Digit Health.* 2020; 2(10):e526-e536.
4. Poplin R, Varadarajan AV, Blumer K, et al. Prediction of cardiovascular risk factors from retinal fundus photographs via deep learning. *Nat Biomed Eng.* 2018; 2(3):158-164.
5. Vaghefi E, Yang S, Hill S, et al. Detection of smoking status from retinal images; a convolutional neural network study. *Sci Rep.* 2019; 9(1):7180.
6. Gerrits N, Elen B, Craenendonck TV, et al. Age and sex affect deep learning prediction of cardiometabolic risk factors from retinal images. *Sci Rep.* 2020; 10(1):9432.
7. Mitani A, Huang A, Venugopalan S, et al. Detection of anaemia from retinal fundus images via deep learning. *Nat Biomed Eng.* 2020; 4(1):18-27.
8. Sabanayagam C, Xu D, Ting DSW, et al. A deep learning algorithm to detect chronic kidney disease from retinal photographs in community-based populations. *Lancet Digit Health.* 2020; 2(6):e295-e302.
9. Kang EY, Hsieh YT, Li C, et al. A deep learning model for detecting early renal function impairment using retinal fundus images: model development and validation study [preprint]. *JMIR Med Informatics.* 2020; 8(11):e23472.
10. Cheung CY, Xu D, Cheng CY, et al. A deep-learning system for the assessment of cardiovascular disease risk via the measurement of retinal-vessel calibre. *Nat Biomed Eng.* 2021; 5(6):498-508.
11. Lim G, Lim ZW, Xu D, et al. Feature isolation for hypothesis testing in retinal imaging: an ischemic stroke prediction case study. Proceedings of the AAAI Conference on Artificial Intelligence. 2019; 33(01):9510-9515.
12. Son J, Shin JY, Chun EJ, et al. Predicting high coronary artery calcium score from retinal fundus images with deep learning algorithms. *Trans Vis Sci Technol.* 2020; 9(2):28.
13. Rim TH, Lee CJ, Tham YC, et al. Deep-learning-based cardiovascular risk stratification using coronary artery calcium scores predicted from retinal photographs. *Lancet Digit Health.* 2021; 3(5):e306-e316.
14. Chang J, Ko A, Park SM, et al. Association of cardiovascular mortality and deep learning-funduscopic atherosclerosis score derived from retinal fundus images. *Am J Ophthalmol.* 2020; 217:121-130.
15. Wagner SK, Fu DJ, Faes L, et al. Insights into systemic disease through retinal imaging-based oculomics. *Transl Vis Sci Technol.* 2020; 9(2):6.

AI-Based Fluid Monitoring in Clinical Practice

Ursula Schmidt-Erfurth MD

Clinical Needs in Respect to Managing Macular Fluid

Macular disease associated with retinal fluid and its detrimental consequence of severe and irreversible visual loss is a major focus of health-care efforts and clinical as well as basic research. Its medical and socioeconomic dimension is overwhelming: More than 600 million individuals older than 65 years in 2015 and an increase of the elderly population by 236 million over the next 10 years are at high risk for developing AMD. This trend coincides with a global pandemic of similar extent due to diabetes mellitus currently affecting about 420 million adults, rising to more than 800 million by 2030, according to the World Health Organization, of which a third will experience vision-threatening diabetic maculo- and retinopathy. World-wide vision loss increased by 23% for blindness and 24% for severe vision loss between 2005 and 2015, in total affecting 900 million individuals despite significant advances in diagnostic and therapeutic tools. Moreover, Medicare payments per beneficiary for eye care alone have doubled for the cohort of AMD patients, with most of the billing increase due to anti-VEGF injections.

During COVID times, a substantial movement toward disease management solely based on OCT imaging has taken place, according to the ASRS survey 2020. However, OCT evaluation by human experts is time consuming and subjective and lacks an objective quantitative measurement. The largest database from real-world outcomes originates from the United States Electronic Health Records database and is comprised of functional and morphological outcomes from 30,106 neovascular AMD (nAMD) patients. Compared to the performance of physicians in clinical trials using identical diagnostic and therapeutic hardware tools, the report suggested that "treating physicians may be the root cause" of real-world suboptimal outcomes. Algorithms using methods of artificial intelligence (AI), such as deep learning, provide accurate detection, localization, and quantification of all types of macular fluid and are offering ideal tools for precision management in the clinical routine, empowering the physicians.

Requirements for a Useful AI-Based Fluid Quantification

Localization of retinal fluid and volume quantification fundamentally relies on accurate AI-based "image segmentation" methods, which assign to the respective OCT voxels a label denoting the fluid-type (see Figure 1).

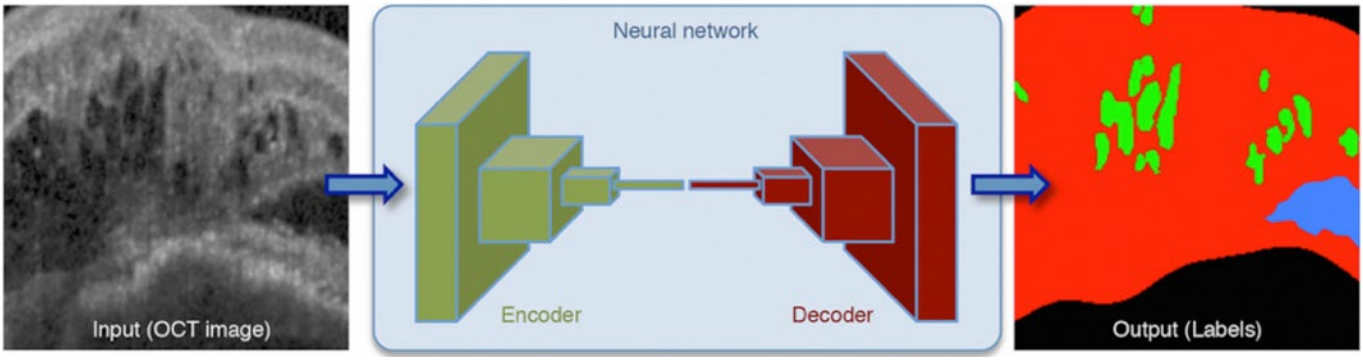


Figure 1

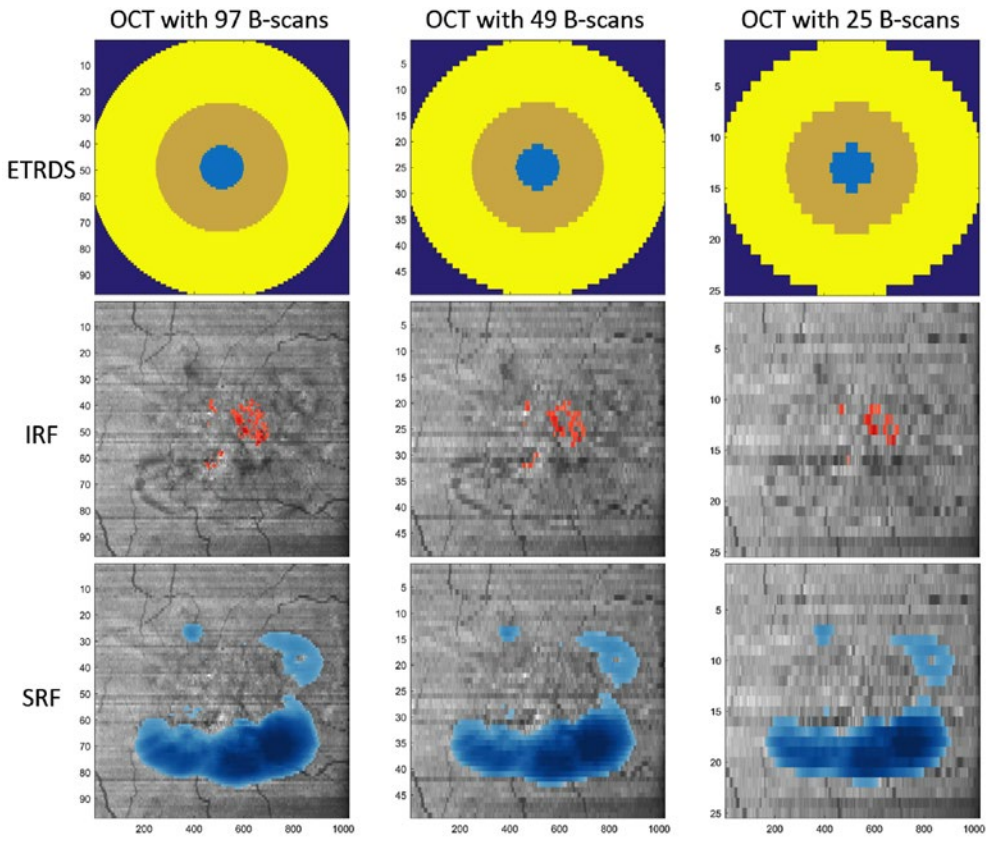


Figure 2

After localizing the fluid in a volumetric scan, a 2-dimensional en face topographic map of fluid distribution in the macula can be computed and displayed, as in Figure 2.

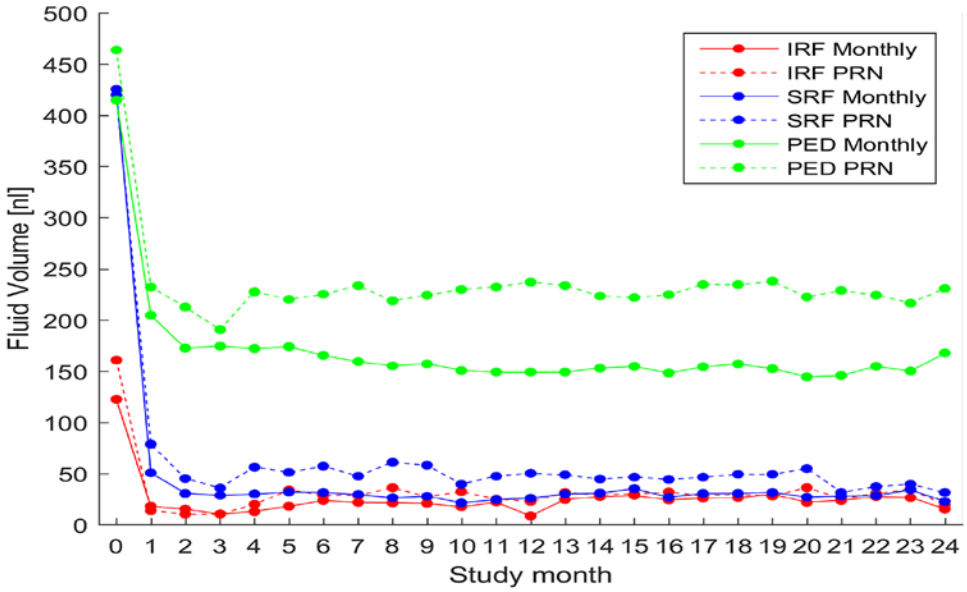
This allows us to quantify the volume of the identified fluid, not only for an entire OCT scan, but for a specific local region spatially defined by an ETDRS grid. Fluid volumes are most commonly expressed in nanoliter (nL) units. The estimates of volume quantities are tightly coupled with the spatial resolution of the acquired OCT scan because the number of acquired OCT B-scans and the physical spacing between them can vary between different imaging settings and different OCT device manufacturers. Convolutional neural networks (CNNs) allow segmentations to be obtained from images of arbitrary sizes and directly translate the input OCT image into the output image of labels. CNN can be adapted to specific OCT device vendor and macular disease.

For AI-based fluid assessment to provide an effective clinical decision support, in addition to an appropriate OCT scanning pattern, several further aspects have to be taken into consideration. Due to the large amount of fluid pockets potentially present in a scan, the assessment methods should be fully automated, as even minimally interactive approaches would be too labor-intensive. Furthermore, a fully automated assessment ensures an objective and repeatable fluid quantification. Finally, the runtime of the AI algorithm should be short, and clinical workflow integration should be tight enough to avoid contributing to an increase in the duration of an eye examination during a standard clinical visit. Ideally, a complete assessment of fluid should be accessible in real time by a mouse click only.

Insights From AI-Based Fluid Monitoring in Clinical Trials

In the HARBOR trial—a randomized 24-month, Phase 3 study evaluating the efficacy of ranibizumab with different dosages (0.5 and 2.0 mg) and different regimens (fixed monthly and p.r.n.)—macular fluid volumes from 1095 patients were analyzed. Macular fluid was automatically identified, quantified, and classified into intraretinal fluid (IRF), subretinal fluid (SRF), or pigment-epithelial detachment (PED) using deep learning. IRF volumes dramatically decreased after the first injection and remained on a low level in both the monthly and p.r.n. treatment arms. SRF also decreased significantly after the first injection; however, SRF persisted in higher volumes compared to IRF throughout the study. In contrast, subretinal PED decreased to about half its baseline volume, and resolution was dependent on the injection regimen. In conclusion, a dose and regimen effect was precisely quantifiable with deep learning when assessing macular fluid under anti-VEGF therapy. IRF was found to be the most important influencer for BCVA loss. See volumes in HARBOR in Figure 3.

Figure 3



The FLUID study was a 24-month, Phase 4, randomized, multicenter study, investigating the clinical tolerance of SRF to a maximum height of 200 µm at the foveal center in a treat-and-extend regimen. The primary goal was to investigate non-inferiority of visual acuity (VA) between SRF-tolerant and SRF-intolerant treatment arms. A subsequent AI-based quantitative analysis showed that the reduction of injections was in fact not associated with the expected higher volumes of (tolerated) SRF, and that quantified SRF volumes did not differ between the treatment arms. In general, residual SRF volumes further increased to the subsequent visit when tolerated. Furthermore, VA declined at the visit subsequent to SRF-tolerance, indicating a worsening in BCVA, at least in the short term. This suggests that SRF has an impact on BCVA that is volume dependent.

HAWK and HARRIER were Phase 3, 2-year, multicenter, randomized clinical trials assessing the efficacy and safety of brolucizumab 6 mg/3 mg against aflibercept 2 mg after a loading phase of 3 injections. Aflibercept was administered bimonthly, whereas brolucizumab was planned every 12 weeks with a possible bimonthly rescue. OCT assessments were performed at every visit, and automated detection and quantification of macular fluid volumes was performed subsequently. IRF was similarly and significantly decreased after the first injection in both the brolucizumab and aflibercept arms. Under brolucizumab treatment, SRF and PED volumes decreased more than with aflibercept, demonstrating a more intensive and stable reduction throughout the maintenance period. Moreover, lower volumes of all types of macular fluid resulted in superior visual outcome compared to higher volumes of any residual fluid, especially IRF, but also SRF and PED. The conclusion of this quantified fluid analysis confirmed that all fluid types matter in the management of macular disease.

AI in Real-World Fluid Analysis

Macular fluid assessment is the best opportunity to use the full potential of 3-dimensional OCT images that are used every day in busy clinics. Real-world outcomes are crucial for an unbiased understanding of disease activity and therapeutic response. Yet only few analyses using AI in retina are available so far:

- Moraes et al applied a deep learning algorithm for automated quantification to OCT images from the Moorfields Eye Hospital AMD Database in eyes with nAMD at baseline presentation, but not under therapy. A total of 2473 first-treated eyes and 493 second-treated fellow eyes were included. Volumes were segmented and calculated for multiple features, such as neurosensory retina (NSR), drusen, IRF, SRF, subretinal hyperreflective material, retinal pigment epithelium (RPE), hyperreflective foci, fibrovascular PED (fvPED), and serous PED (sPED). In conclusion, first-treated eyes had greater volumes for all segmented tissues, with the exception of drusen, and older age was associated with lower volumes for RPE, SRF, NSR, and sPED. Greater volumes of the majority of features were associated with worse VA. Fluid volumes did not follow a linear regression, which makes the interpretation of this analysis difficult.
- Keenan et al evaluated retinal fluid volume data extracted from OCT scans by AI algorithms from different clinical trials and real-world settings. Interestingly, wide ranges that differed by population were observed at the treatment-naïve stage. Mean volumes in each compartment decreased rapidly and consistently under anti-VEGF therapy under standardized trial conditions as well as in real-world scenarios. During the maintenance therapy, mean IRF volumes under therapy showed substantial differences in the analyzed data sets, particularly for IRF. Yet fluid quantification also demonstrated less control on fluid in real-world settings. This detailed comparison of different settings highlights the variability in individual populations and the influence of variable treatment patterns.
- Chakravarthy et al studied the effect of fluid volume fluctuations during anti-VEGF maintenance in nAMD. Data were extracted from electronic medical records of 381 nAMD patients, aged ≥50 years; baseline VA ≥33

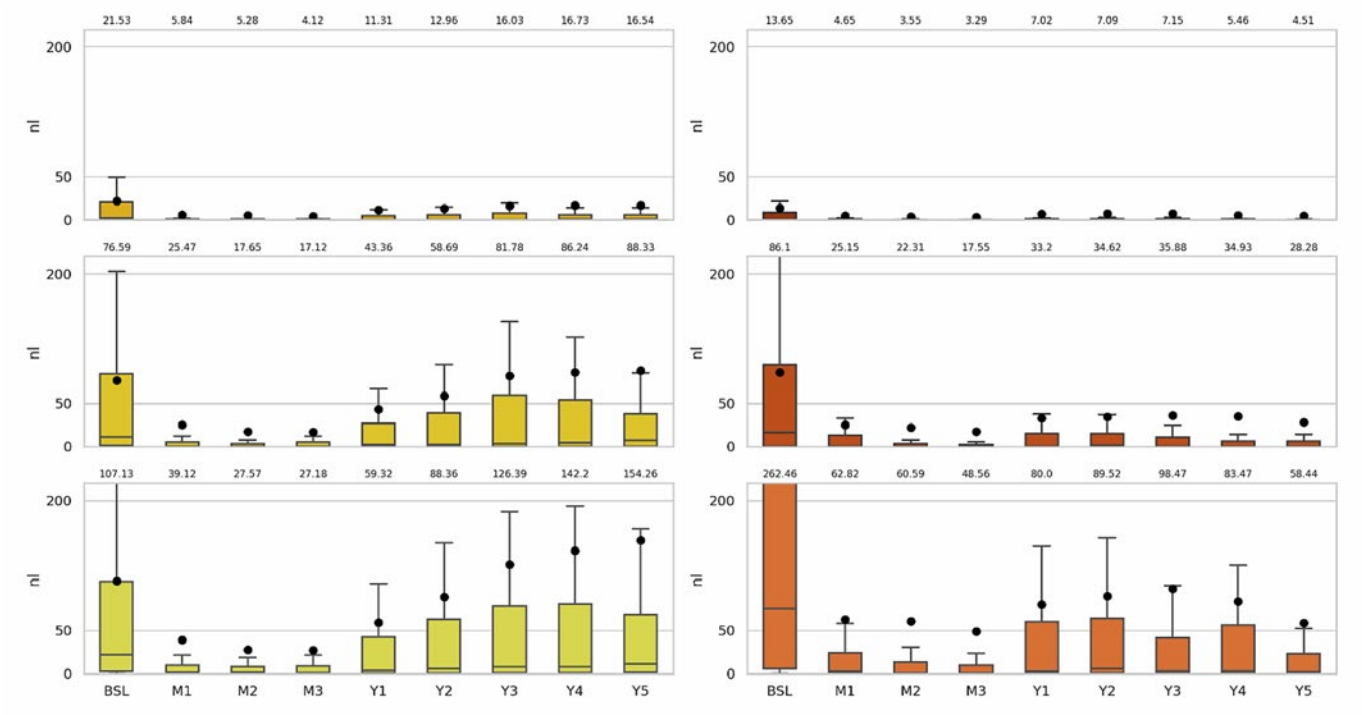


Figure 4

and ≤73 letters; ≥24 months follow-up and ≥2 OCT measurements. OCT scans were analyzed using an AI algorithm that quantified the volumes of IRF, SRF, PED, and central subfield thickness. As a measure for volume fluctuations, the standard deviations (SD) were computed and categorized into quartiles (SD-Q1-4). However, SDs from the a priori small volumes resulted in very low fluid amounts and were based on few (>2) visits with widely variable intervals over 24 months. BCVA was significantly lower after 2 years in eyes experiencing most fluctuations in CRT. IRF had the greatest impact on function and SRF the lowest.

- Gerendas et al performed deep learning–based automated fluid quantification in real-world clinical routine OCT images in nAMD over 4 years of follow-up. Data from the Vienna Imaging Biomarker Eye Study (VIBES) registry from 2007-2018 (electronic patient record, treatment database, and 2 OCT devices) were analyzed using the Vienna fluid monitor, an automated fluid segmentation tool based on deep learning. Matching all entries and filtering for active nAMD by baseline OCT for automated IRF, SRF, and central subfield thickness segmentation led to inclusion of 1127 eyes. IRF and SRF volumes were at their maximum at baseline in the central 1, 3, and 6 mm. IRF decreased to a mean of 4-5 nL at Month 1-3 in the 1-mm area and increased to 11 nL at Year 1 and to 16 nL at Year 5. SRF decreased to a mean of 3-5 nL at Month 1-3 in the 1-mm area and remained below 7 nL until Year 5. IRF was the only parameter to symmetrically reflect the course of VA change over time. Fluid control was optimal during the loading dose, and volumes increased only slightly and in a stable manner over the following years in this real-world treat-and-extend regimen (see Figure 4).

A ground truth validation by the readers of the Vienna Reading Center confirmed the findings from automated analyses. This work provided proof-of-principle that deep learning–based automated fluid quantification in clinical routine images is well suited to objectively, reliably, and rapidly measure treatment response and optimally guide clinical management in nAMD. Moreover, the fluid monitor introduced reading center expertise and substantial time savings into clinical routine. Automated volume measurements in a real-world dataset over a period of many years suggested IRF volume as an ideal guidance for optimal treatment decisions.

The Vienna Fluid Monitor

A deep learning–based tool to locate and quantify fluid volumes, the Vienna fluid monitor (AI-based Fluid Monitor, RetInSight; Vienna, Austria), has been trained extensively on real-world OCT images and underwent a thorough evaluation by human expert clinicians. In an independent setting, the fully automated algorithm underwent CE certification for use in clinical routine. In a consecutive step, the advanced tool was introduced into clinical practice in several large scale outpatient macular clinics and evaluated for the management of nAMD under an approved clinical protocol. Patients with active nAMD undergo conventional anti-VEGF therapy in a 2-arm comparison with either retreatment decisions based on state-of-the-art clinicians' discretion or decision support by automated fluid volume localization and quantification. An en face map demonstrates the distribution of fluid by IRF/SRF type on an ETDRS grid. A complete fly-through offers the full original B-scan volume and the representation of the fluid segmentations. The accurate volumes in nanoliters for the central 1 and 6 mm are listed in a table, together with the relative increase or decrease by compartment. A graph over time indicates the time

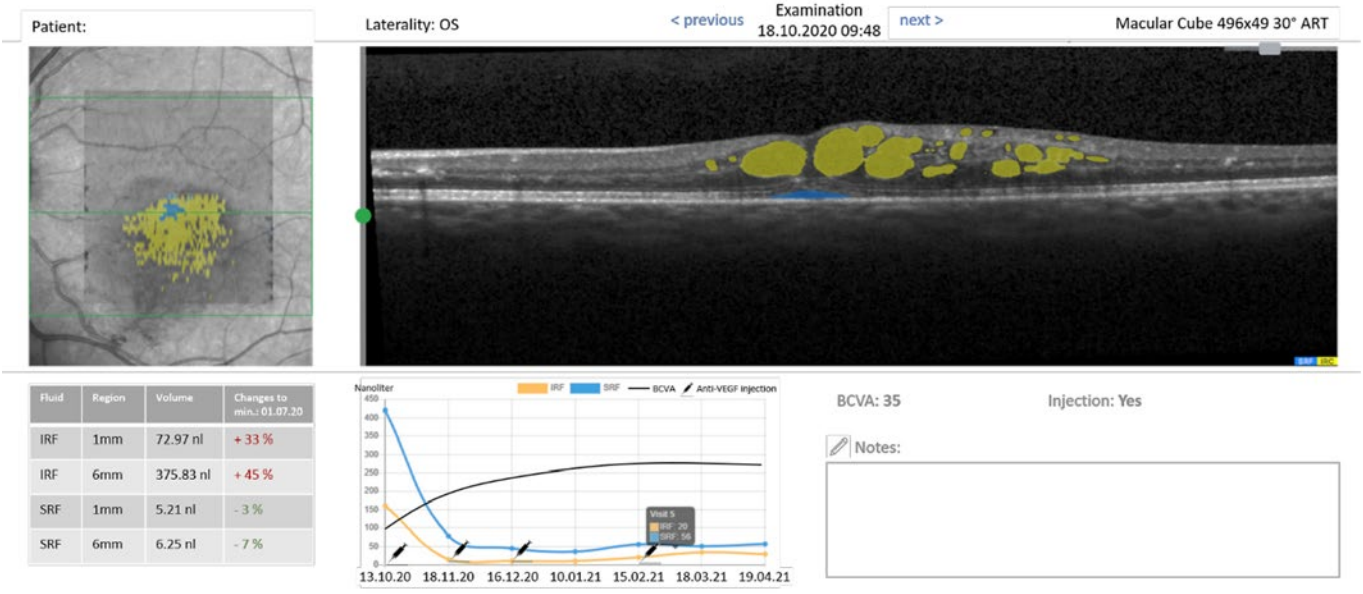


Figure 5

course of BCVA and IRF/SRF volumes throughout all visits, with an interactive interface allowing access to the fluid data for each time point (see Figure 5). The tool offers real-time fluid analyses during each individual patient visit and is accessible at any practice or clinic location by the cloud.

The use of the fluid monitor includes a wide spectrum of opportunities:

- Clinical trial support offering real-time fluid quantification on site in multicenter clinical trials, thereby implementing distinct adherence to the study protocols without the previous discrepancies between investigators' judgements
- Screening for conversion to an exudative stage in patients with intermediate AMD at risk and second eye follow-up
- Monitoring of patients under anti-VEGF therapy, allowing precision management and the introduction of clinically relevant parameter definitions such as IRF vs. SRF, including adequate thresholds to capture recurrence

References

1. Chakravarthy U, Havilio M, Syntosi A, et al. Impact of macular fluid volume fluctuations on visual acuity during anti-VEGF therapy in eyes with nAMD. *Eye (Lond)*. Epub ahead of print 2021 Jan 7. doi.org/10.1038/s41433-020-01354-4.
2. Grechenig C, Arnold JJ, Bogunovic H, et al. Automated quantification of retinal fluid and its impact on treatment outcomes in the FLUID study. *Invest Ophthalmol Vis Sci*. 2020; 61:3507.
3. Keenan TDL, Chakravarthy U, Loewenstein A, Chew EY, Schmidt-Erfurth UM. Automated quantitative assessment of retinal fluid volumes as important biomarkers in neovascular age-related macular degeneration. *Am J Ophthalmol*. 2021; 224:267-281.
4. Moraes G, Fu DJ, Wilson M, et al. Quantitative analysis of OCT for neovascular age-related macular degeneration using deep learning. *Ophthalmology* 2021; 128(5):693-705.
5. Reiter GS, Grechenig C, Vogl W-D, et al. Analysis of fluid volume and its impact on visual acuity in the FLUID study as quantified with deep learning. *Retina* 2021; 41(6):1318-1328.
6. Schmidt-Erfurth U, Vogl WD, Jampol LM, Bogunović H. Application of automated quantification of fluid volumes to anti-VEGF therapy of neovascular age-related macular degeneration. *Ophthalmology* 2020; 127(9):1211-1219.
7. Schmidt-Erfurth UM, Sadeghipour A, Gerendas BS, Waldstein SM, Bogunović H. Artificial intelligence in retina. *Prog Retin Eye Res*. 2018; 67:1-29.
8. Schmidt-Erfurth U, Reiter GS, Riedl S, et al. AI-based monitoring of retinal fluid in disease activity and under therapy. *Prog Retin Eye Res*. Epub ahead of print 2021 Jun 22;100972. doi: 10.1016/j.preteyeres.2021.100972.

Clinician-Driven Machine Learning: A New Phase for AI-Enabled Health Care?

Pearse A Keane MBBCh

Artificial intelligence (AI)—in particular a technique referred to as "deep learning"—has the potential to transform health care. Until recently, however, the development of cutting-edge AI in health care required highly specialized technical expertise. Fortunately, in recent years, we have seen the introduction of "code-free" deep learning platforms, typically with drag-and-drop interfaces, that allow development of AI tools with minimal technical expertise. Using these platforms, clinical researchers have been able to develop AI tools for skin cancer, chest x-rays, retinal photographs, and OCT, often with results comparable to those of state-of-the-art technology. In the coming years, this democratization of AI will continue allowing domain experts such as ophthalmologists to play an increasing role in a new phase of AI-enabled health care. In my presentation, I will give an overview of these platforms and describe how they are likely to be used in ophthalmic research in the coming years.

New Instrumentation for Vitreoretinal Surgery

David R Chow MD

NOTES

Vision-Degrading Myodesopsia

J Sebag MD FACS FRCOphth FARVO

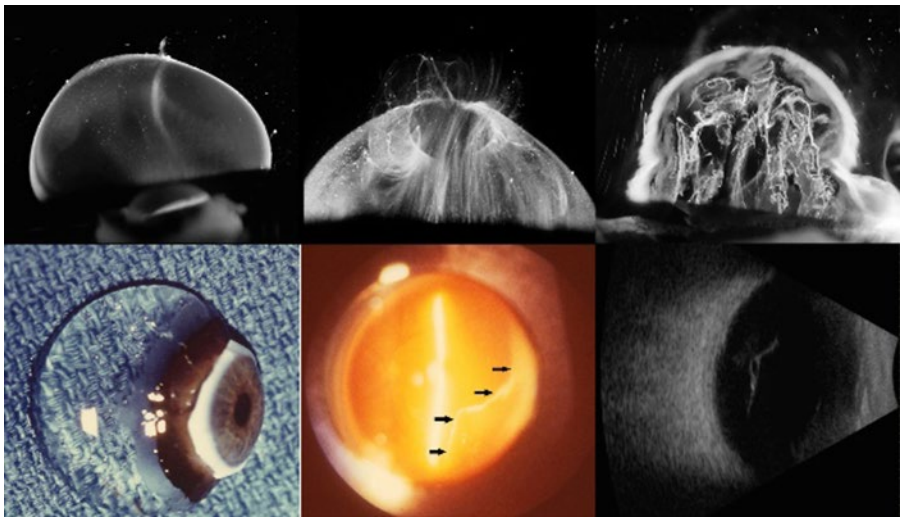


Figure 1

I. Introduction[1]
II. Etiology
  A. Myopic vitreopathy[2]
  B. Posterior vitreous detachment[3]
III. Diagnostic Criteria
  A. Physical examination
  B. Ultrasonography[4]
  C. Contrast sensitivity function[5,6]
IV. Therapeutic Options
  A. YAG laser[7]
  B. Vitrectomy[8,9]
V. Future Developments
  A. Diagnostic: OCT[10,11]
  B. Therapeutic
    1. Nanobubble vitreolysis[12,13]
    2. Pharmacologic vitreolysis[14,15]

References

1. Sebag J. Vitreous and vision degrading myodesopsia. *Prog Ret Eye Res*. 2020; 79:100847.
2. Nguyen JH, Nguyen-Cuu, Mamou J, Routledge B, Yee KMP, Sebag J. Vitreous structure and visual function in myopic vitreopathy. *Am J Ophthalmol*. 2021; 224:246-253.
3. Sebag J. Posterior vitreous detachment. *Ophthalmology* 2018; 125:1384-1385.
4. Mamou J, Wa CA, Yee KM, et al. Ultrasound-based quantification of vitreous floaters correlates with contrast sensitivity and quality of life. *Invest Ophthalmol Vis Sci*. 2015; 56:1611-1617.
5. Garcia G, Khoshnevis M, Yee KM, Nguyen-Cuu J, Nguyen JH, Sebag J. Degradation of contrast sensitivity following posterior vitreous detachment. *Am J Ophthalmol*. 2016; 172:7-12.
7. Garcia G, Khoshnevis M, Nguyen-Cuu J, et al. The effects of aging vitreous on contrast sensitivity function. *Graefes Arch Clin Exp Ophthalmol*. 2018; 256:919-925.
8. Nguyen JH, Nguyen-Cuu J, Yu F, et al. Assessment of vitreous structure and visual function after Nd:YAG laser vitreolysis. *Ophthalmology* 2019; 126(11):1517-1526.
6. Sebag J, Yee KMP, Huang L, Wa C, Sadun AA. Vitrectomy for floaters—prospective efficacy analyses and retrospective safety profile. *Retina* 2014; 34:1062-1068.
7. Sebag J, Yee KMP, Nguyen JH, Nguyen-Cuu J. Long-term safety and efficacy of vitrectomy for vision degrading myodesopsia from vitreous floaters. *Ophthalmol Retina*. 2018; 2(9):881-887.
8. Hwang ES, Kraker JA, Griffin KJ, et al. Accuracy of spectral domain OCT of the macula for detection of complete posterior vitreous detachment. *Ophthalmol Retina*. 2020; 4(2):148-153.
9. Ruminski D, Sebag J, Toledo RD, et al. Volumetric optical imaging and quantitative analysis of age-related changes in anterior human vitreous. *Invest Ophthalmol Vis Sci*. 2021; 62(4):31.
10. Sauvage F, Fraire JC, Remaut K, et al. Photoablation of human vitreous opacities by light-induced vapor nanobubbles. *ACS Nano*. 2019; 13(7):8401-8416.
11. Baras A, Sauvage F, de Hoon I, et al. Carbon quantum dots as a dual platform for the inhibition and light-based destruction of collagen fibers: implications for the treatment of eye floaters. *Nanoscale Horiz*. 2021; 6(6):449-461.
12. Sebag J. Pharmacologic vitreolysis—premise and promise of the first decade [guest editorial]. *Retina* 2009; 29:871-874.
13. Sebag J. Pharmacologic vitreolysis. In: Sebag J, ed. *Vitreous: In Health and Disease*. New York: Springer; 2014:799-816.

Management of Myopic Traction Maculopathy

Barbara Parolini MD

Introduction

Pathologic myopia (PM), commonly referring to refractive error greater than –6.00 D and eyes with axial length (AL) >26.00 mm, has a prevalence of 2% in adults older than 40 years of age, especially in certain areas of the world.[1] Myopic traction maculopathy (MTM) is one of the vision-threatening consequences that may develop from PM. The natural history of MTM, as well as all the possible evolutions of the disease, have recently been described by our group.[3]

Although different authors have reported proposals of treatment with pars plana vitrectomy (PPV)[4] or macular buckle (MB),[5] comprehensive guidelines of management, from studies with long-term follow-up, are still missing, and the choice of the best treatment is still controversial. The goals of surgery must be anatomical and functional: The anatomical goals should be retinal attachment and hole closure. The functional goals should be to improve or maintain central vision and the central visual field. The primary aim of the present study was to report the anatomical response of tissue to treatment with MB, PPV, or the 2 techniques combined. Unlike previously published papers, the present study analyzed the results of each treatment, in each stage of MTM, according to the new MTM Staging System (MSS), in order to propose customized treatment per stage. The secondary aim was to report the functional results after treatment.

Methods

The data of 281 eyes, operated for MTM in different stages, were retrospectively reviewed, and 157 with 2 years follow-up were selected for this study. The analysis was performed after collecting preoperative data on age, sex, eye, decimal BCVA, AL measurement, wide-field color fundus photography, and OCT. The macular buckle technique is described elsewhere.[6]

Results

Table 1 summarizes the demographic data of the eyes in our study. The anatomical and functional results were analyzed per each stage according to the MSS. Table 2 reports the change in BCVA. Tables 3-6 represent the anatomical intermediate and final results divided per stage and per surgery type.

Table 1. Demographic and Clinical Data of Patients

MSS Stage (Retinal Pattern)	No. of Eyes (% of Total)	Age in Years (Mean ± *SD*)	Baseline BCVA, Dec. (Mean ± SD)	Axial Length in mm (Mean ± SD)	MSS Stage (Foveal Pattern)		
					A: No. of Eyes (%)	B: No. of Eyes (%)	C: No. of Eyes (%)
1	33 (21)	53.1 ± 9.2	0.33±0.20	32.25 ± 1.7	16 (10)	9 (6)	8 (5)
2	44 (27)	58.6 ± 10.6	0.21±0.20	31.1 ± 2.1	16 (10)	27 (17)	1 (1)
3	48 (31)	62.25 ± 9.4	0.16±0.14	32 ± 2.2	28 (18)	13 (8)	7 (4)
4	32 (20)	61 ± 10.9	0.12±0.12	29.9 ± 1.9	12 (8)	3 (2)	17 (11)
Total	157	58.74 ± 10.25	0.20±0.18	31.2 ± 2.3	72 (46)	52 (33)	33 (21)

Table 2. Average BCVA—Preoperative and at the Final Follow Up

MSS Stage	BCVA Preop (Decimal)	BCVA Final (Decimal)
1a	0.42	0.58
1b	0.34	0.5
1c	0.12	0.35
2a	0.27	0.39
2b	0.17	0.25
2c	0.1	0.2
3a	0.35	0.41
3b	0.25	0.38
3c	0.13	0.27
4a	0.15	0.28
4b	0.2	0.33
4c	0.08	0.19

Table 3. Results, Stage 1

Stage 1		Retina		Fovea	
Surgery	Outcome	Intermediate No. (% of Surgical Group)	Final No. (% of Surgical Group)	Intermediate No. (% of Surgical Group)	Final No. (% of Surgical Group)
MB, No. (%)	Resolved	0	14 (100)	1 (7)	13 (93)
	Improved	14 (100)	0	9 (64)	0
	Unchanged	0	0	2 (14)	1 (7)
	Worsened	0	0	2 (14)	0
	Total	14			
PPV, No. (%)	Resolved	10 (71)	14 (100)	10 (71)	13 (93)
	Improved	4 (29)	0	3 (22)	0
	Unchanged	0	0	1 (7)	1 (7)
	Worsened	0	0	0	0
	Total	14			
MB+PPV, No. (%)	Resolved	5	5 (100)	4 (80)	5 (100)
	Improved	0	0	1 (20)	0
	Unchanged	0	0	0	0
	Worsened	0	0	0	0
	Total	5			
P < .05		.0051	.0051	.0614	.3187

Table 4. Results, Stage 2

Stage 2		Retina		Fovea	
Surgery	Outcome	Intermediate No. (% of Surgical Group)	Final No. (% of Surgical Group)	Intermediate No. (% of Surgical Group)	Final No. (% of Surgical Group)
MB, No. (%)	Resolved	11 (40)	26 (90)	5 (17)	23 (79)
	Improved	16 (55)	2 (7)	12 (41)	2 (7)
	Unchanged	2 (7)	1 (3)	8 (28)	4 (14)
	Worsened	0	0	4 (14)	0
	Total	29			
PPV, No. (%)	Resolved	0	2 (66)	0 (0)	2 (66)
	Improved	1 (33)	1 (33)	1 (33)	1 (33)
	Unchanged	1 (33)	0	1 (33)	0
	Worsened	1 (33)	0	1 (33)	0
	Total	3			
MB+PPV, No. (%)	Resolved	11 (92)	12 (100)	9 (76)	11 (92)
	Improved	1 (8)	0	1 (8)	1 (8)
	Unchanged	0	0	1 (8)	0
	Worsened	0	0	1 (8)	0
	Total	12			
P < .05		.0004	.2813	.0333	.1537

Table 5. Results, Stage 3

Stage 3		Retina		Fovea	
Surgery	Outcome	Intermediate No. (% of Surgical Group)	Final No. (% of Surgical Group)	Intermediate No. (% of Surgical Group)	Final No. (% of Surgical Group)
MB, No. (%)	Resolved	10 (56)	18 (100)	8 (44)	16 (89)
	Improved	8 (44)	0	7 (39)	0
	Unchanged	0	0	3 (17)	2 (11)
	Worsened	0	0	0	0
	Total	18			
PPV, No. (%)	Resolved	4 (22)	18 (100)	0	18 (100)
	Improved	1 (6)	0	0	0
	Unchanged	2 (11)	0	2 (12)	0
	Worsened	11 (61)	0	15 (88)	0
	Total	18			
MB+PPV, No. (%)	Resolved	8 (69)	12 (100)	5 (38.5)	11 (92)
	Improved	3 (23)	0	3 (23)	0
	Unchanged	1 (8)	0	0	1 (8)
	Worsened	0	0	4 (38.5)	0
	Total	12			
P < .05		<.0001	.2946	<.0001	.3857

Table 6. Results, Stage 4

Stage 4		Retina		Fovea	
Surgery	Outcome	Intermediate No. (% of Surgical Group)	Final No. (% of Surgical Group)	Intermediate No. (% of Surgical Group)	Final No. (% of Surgical Group)
MB, No. (%)	Resolved	18 (82)	21 (95)	16 (73)	18 (82)
	Improved	2 (9)	1 (4)	4 (18)	2 (9)
	Unchanged	1 (4)	0	2 (9)	2 (9)
	Worsened	0	0	0	0
	Total	22			
PPV. No. (%)	Resolved	0	1 (100)	0	1 (100)
	Improved	0	0	0	0
	Unchanged	0	0	0	0
	Worsened	1 (100)	0	1 (100)	0
	Total	1			
MB+PPV, No. (%)	Resolved	9 (100)	8 (89)	8 (89)	7 (78)
	Improved	0	0	0	0
	Unchanged	0	1 (11)	1 (11)	2 (22)
	Worsened	0	0	0	0
	Total	9			
P < .05		< .0001	.5044	< .0001	.7019

Conclusions

The key issue of the present study was to clarify how to choose the best management for each MSS stage, selecting among 4 possible options: observation, PPV, MB, or combined MB+PPV. Our choice was built on the evaluation of the anatomical and functional results balanced with the specific complications of the 2 approaches.

By looking at the image of forces exerted on the retina (Figure 1) in MTM eyes, it becomes clear how treatment should counteract the centrifugal forces that tend to detach the retina from the eyewall, and to change the retinal pattern perpendicularly, and/or the centrifugal forces that tend to split the macula, and to change the foveal pattern tangentially.

The conclusion of our study was the proposal of the MSS Management (MSS-Man) Table (Figure 2).

Stages 1a, 2a, and 3a should be followed with observation every 12 to 18 months, since BCVA in these groups is still good and the progression is slow, unless epiretinal abnormalities are associated. The symptomatic cases should be treated like cases of epiretinal membrane without MTM.

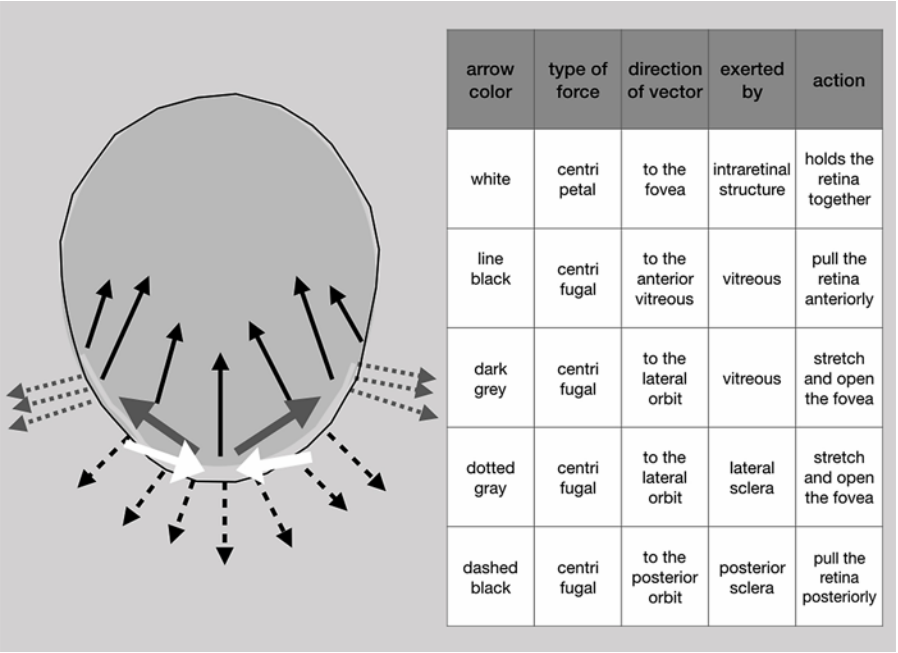
A high rate of anatomical success could be reached when PPV was used for Stage 1b, 1c, 2b, and 2c. MB should be considered and evaluated case by case in stage 3b. MB and late subsequent PPV were revealed particularly useful in Stage 3b, even in eyes with macular atrophy, obtaining a gain in visual function when the schisis and the inner lamellar macular hole (I-LMH) were resolved with restoration of the retina and foveal pattern.

Our recommendation is to treat the retinal pattern first, with the buckle, and then to treat the foveal pattern with PPV, later on, only if required by lack of improvement of visual acuity or by progression of the I-LMH. Stages MSS 4a, 4aO, 4b, 4bO, 5a, 5aO, and 5b should be treated immediately with a MB alone. PPV might be added to stages b later on, only if needed. Stages MSS 4c, 5bO, and 5c should be immediately treated with combined MB+PPV in order to treat simultaneously the retinal and the foveal patterns.

Observing the anatomical answer to the different treatments in every stage, we could clearly observe how PPV addressed the tangential tractions on the inner retinal surface and how the MB addressed the perpendicular tractions on the retina induced by scleral elongation.

Treating a prevalent tangential traction with a MB leads to potential complications as well as does treating a prevalent perpendicular traction with PPV. Also, treating only one component of traction allows the opposite component to manifest itself in time. Knowing which treatment to choose in a customized fashion based on the MTM Staging Table allows for a long-lasting benefit to the patient.

The MSS Management Table offers guidelines for follow-up and types of treatment.



arrow color	type of force	direction of vector	exerted by	action
white	centri petal	to the fovea	intraretinal structure	holds the retina together
line black	centri fugal	to the anterior vitreous	vitreous	pull the retina anteriorly
dark grey	centri fugal	to the lateral orbit	vitreous	stretch and open the fovea
dotted gray	centri fugal	to the lateral orbit	lateral sclera	stretch and open the fovea
dashed black	centri fugal	to the posterior orbit	posterior sclera	pull the retina posteriorly

Figure 1

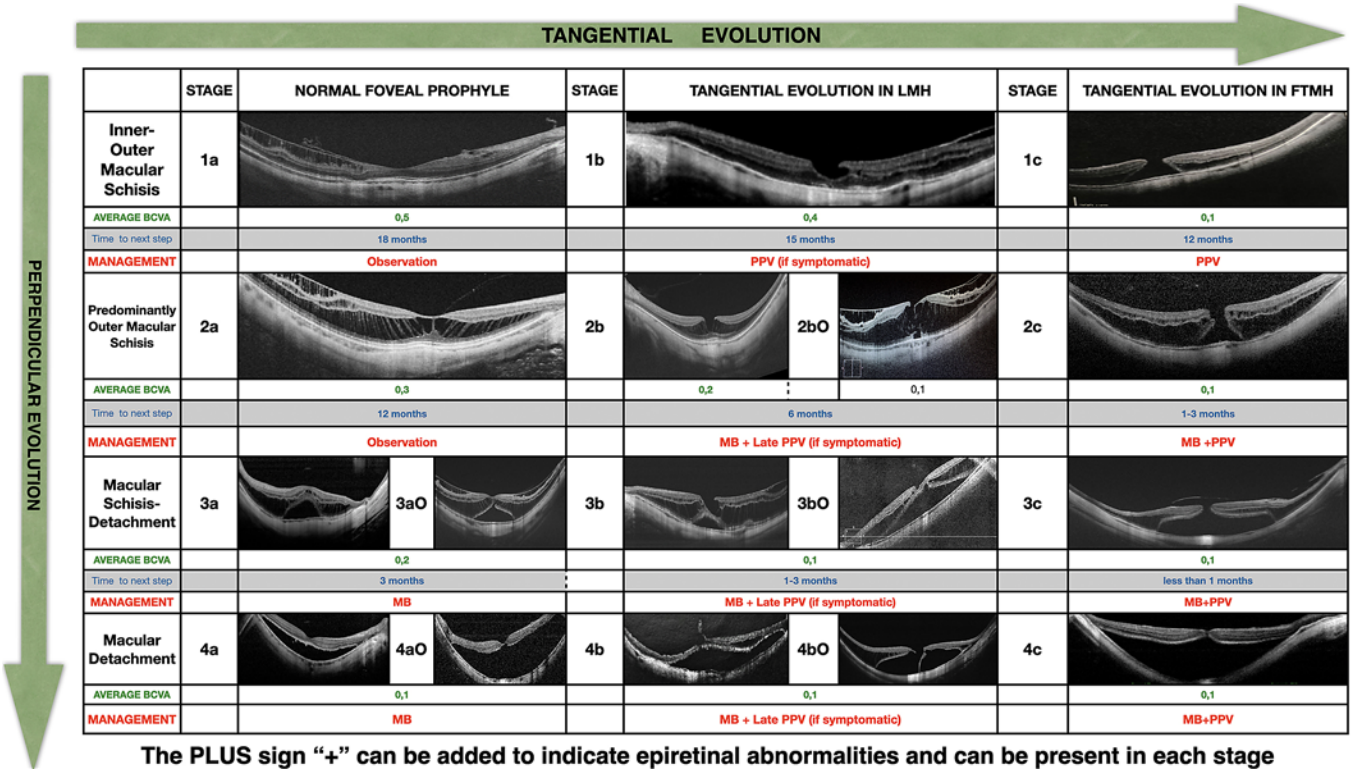


Figure 2. The MSS Management Table.

References

1. Sawada A, Tomidokoro A, Araie M, Iwase A, Yamamoto T. Refractive errors in an elderly Japanese population: the Tajimi study. *Ophthalmology* 2008; 115(2):363-370.e3.
2. Fan DSP, Lam DSC, Lam RF, et al. Prevalence, incidence, and progression of myopia of school children in Hong Kong. *Invest Ophthalmol Vis Sci.* 2004; 45(4):1071-1075.
3. Parolini B, Palmieri M, Finzi A, et al. The new Myopic Traction Maculopathy Staging System. *Eur J Ophthalmol.* 2020 Jun 8;1120672120930590. doi:10.1177/1120672120930590.
4. Kuhn F. Internal limiting membrane removal for macular detachment in highly myopic eyes. *Am J Ophthalmol.* 2003; 135(4):547-549.
5. Parolini B, Frisina R, Pinackatt S, et al. Indications and results of a new L-shaped macular buckle to support a posterior staphyloma in high myopia. *Retina* 2015; 35(12):2469-2482.
6. Parolini B, Frisina R, Pinackatt S, Mete M. A new L-shaped design of macular buckle to support a posterior staphyloma in high myopia. *Retina* 2013; 33(7):1466-1470.

Surgical Techniques for Secondary IOLs

Jonathan L Prenner MD

Although a significant amount of investigation has been undertaken in attempts to identify the optimal approach for secondary IOL placement in patients lacking capsular support, a preferred approach still has not been established. A host of surgical procedures used in the management of these cases exist, including anterior chamber IOLs, scleral-fixated posterior chamber IOLs (PC-IOLs) with or without suture fixation, and iris-fixated PC-IOLs. In 2020, the American Academy of Ophthalmology Ophthalmic Technology Assessment Committee evaluated the literature concerning surgical options for secondary IOLs and concluded that there was no superiority in any particular approach.[1] Interestingly, despite significant developments in instrumentation and technique in the last 15 years, these conclusions were identical to a similarly intended OTA published in 2003.[2]

Each approach to secondary IOL placement can be safe and effective, and all have well-recognized benefits and liabilities. Unfortunately, few prospective, randomized, controlled surgical clinical trials exist to help truly identify a preferred technique. As a result, surgeon preferences and practice patterns remain based on their own training and experience and the evolution of their particular approach.

In this description and video presentation, 3 common techniques used by vitreoretinal surgeons will be presented, including:

1. **Mixed gauge sutureless scleral fixation**. A 25-gauge sutureless vitrectomy is performed. The haptics of a 3-piece secondary IOL are then fixated in the sclera via 27-gauge cannulas. After placement in the intrascleral tunnel, haptic tips are thermally deformed.[3,4]
2. **Gore-Tex fixation of the MX60 (Envista) IOL**. After conjunctival dissection, a small-gauge vitrectomy is performed. Four horizontal sclerotomies are created, and Gore-Tex sutures are thread through the islets of the lens. The sutures are then externalized through the horizontal sclerotomies and tied to secure the lens.[5,6]
3. **30-gauge needle fixation (modified Yamane technique)**. After small-gauge sutureless vitrectomy is performed, an intrascleral tunnel is created with a 30-gauge needle. The leading haptic is then fed into the needle opening, externalized, and thermally deformed. The trailing haptic is then secured in a similar fashion.[7]

Discovery and technique development during the past decade has resulted in advancement of our surgical approaches to secondary IOLs in patients lacking capsular support. Continued work in this space will hopefully lead to novel technologies and procedures that will continue to improve patient outcomes.

References

1. Shen JF, Deng S, Hammersmith KM, et al. Intraocular lens implantation in the absence of zonular support: an outcomes and safety update: a report by the American Academy of Ophthalmology. *Ophthalmology* 2020; 127:1234-1258.
2. Wagoner MD, Cox TA, Ariyasu RG, et al. Intraocular lens implantation in the absence of capsular support: a report by the American Academy of Ophthalmology. *Ophthalmology* 2003; 110:840-859.
3. Todorich B, Sterm MS, Kooragayala K, et al. Structural analysis and comprehensive surgical outcomes of the sutureless intrascleral fixation of secondary intraocular lenses in human eyes. *Retina* 2018; 38(suppl 1):S31-S40.
4. Stem MS, Wa CA, Todorich B, et al. 27-gauge sutureless intrascleral fixation of intraocular lenses with haptic flanging: short-term clinical outcomes and a disinsertion force study. *Retina* 2019; 39(11):2149-2154.
5. Su D, Stephens JD, Obeid A, et al. Refractive outcomes after pars plana vitrectomy and scleral fixated intraocular lens with Gore-Tex suture. *Ophthalmol Retina*. 2019; 3:548-552.
6. Watane A, Botsford BW, Sood AB, et al. Scleral-sutured intraocular lens dislocations secondary to eyelet fractures. *Am J Ophthalmol*. 2021; 221:273-278.
7. Yamane S, Sato S, Maruyama-Inoue M, Kadonosono K. Flanged intrascleral intraocular lens fixation with double-needle technique. *Ophthalmology* 2017; 124:1136-1142.

Rho Kinase Inhibition Reduces Photoreceptor Damage After Retinal Detachment: Possible Implications for Gene and Cell Therapy

Marco Zarbin MD PhD FACS, Ellen Townes-Anderson PhD, Eva Halasz MD, and Ilene Sugino MS

I. Retinal detachment (RD) induces synaptic disjunction in rod and cone photoreceptors.

Injury-induced rearrangement of neural circuits in the retina was described by Erickson et al in 1983.[1] After RD, rod presynaptic terminals retract from the outer plexiform layer into the outer nuclear layer, resulting in disjunction of the first synapse in the visual pathway, the photoreceptor-bipolar synapse. Cone photoreceptors also respond to detachment and exhibit shape changes of their presynaptic pedicle and active zone, but they do not retract their terminals.[2] Specifically, the pedicle changes from a pyramidal to a flattened shape, there is loss of the synaptic ribbons, and there is loss of the invaginations of the synaptic membrane induced by synaptic contact with bipolar and horizontal cells. The synaptic ribbon is located at the active zone of the synapse, positioned several nanometers from the presynaptic membrane and tethers 100 or more synaptic vesicles.

II. Synaptic disjunction (rods and cones) occurs within the area of RD and also in extensive areas outside the RD.[3]

A. Disjunction persists (to varying degrees) after retinal reattachment.

B. The extent of synaptic retraction is quantified using binary images. After vitrectomy only, there are only a few retracted presynaptic terminals. In the fellow eye in the area of RD, there are many more retracted terminals stained for synaptophysin. The quantified data show that there is a 3-fold increase in the amount of synaptic retraction in the area of detachment 2 hours after RD compared to the control eye, and there is a 2.6-fold increase in synaptic retraction in the attached areas of the eye undergoing RD compared to control.

C. Hypothesis: RD initiates spreading depolarization (SD) that extends to adjacent attached retina ≥10 mm from the RD. SD causes synaptic disjunction to spread beyond the boundaries of the RD.

1. SD, described initially as cortical spreading depression, is a wave of extreme cellular depolarization that spreads over the cortical surface at a velocity of 3 mm/min.[1] SD waves → large shifts in transcellular ion gradients, cell swelling, and increased extracellular concentrations of neurotransmitters, particularly glutamate.[2] In acute CNS injury (stroke, subarachnoid hemorrhage, traumatic brain injury), SD events are initiated at borders of damaged tissue and cause additional cell death and expansion of injury zone.[3]

2. SD is generated in vivo after rat retinal vessel occlusion.[4]

III. RD induces increased retinal RhoA-GTP within and outside the area of RD.[3]

A. RhoA is a small GTPase associated primarily with cytoskeleton regulation. RhoA regulates cellular morphological polarization.

B. The activated form of RhoA (RhoA-GTP) is increased in the retina as soon as 2 hours after RD.

C. These experiments were done using an in vivo porcine model. Eyes underwent pars plana vitrectomy (PPV). RD was created using BSS in the nasal quadrant, and the fellow eye served as a control (PPV, no RD). The areas of RD had a 2.5-fold increase in RhoA-GTP compared to the corresponding areas of the control eyes.

D. Areas of the retina as far away as 10 mm or more from the RD also showed an increase in activated RhoA compared to the corresponding area of the control eye.

IV. Synaptic disjunction (rods and cones) is inhibited by Rho kinase inhibitors (intravitreal or subretinal injection).[4]

A. There are 2 isoforms of Rho kinase, ROCK 1 and ROCK 2, both of which bind RhoA. ROCK 2 tends to predominate in the CNS. Both proteins are serine/threonine kinases.

B. Through phosphorylation of different substrates, ROCK activity affects many aspects of cell physiology including cytoskeleton modulation, protein synthesis, apoptosis, and synaptic function (eg, via modulation of actomyosin-based contractility).

C. The isoquinoline derivative fasudil and its active metabolite, ripasudil, are so far the only licensed pharmacological ROCK inhibitors for human treatment. The aminopyridine Y-27632 is a more potent ROCK inhibitor than fasudil.

D. We tested the ability of ROCK inhibitors to block RD-associated rod synaptic disjunction. Both eyes underwent PPV + RD. One eye received subretinal ROCK inhibitor; the other did not. Subretinal 10 mM fasudil applied at the time of RD demonstrated a 51% reduction in the extent of synaptic disjunction in detached and adjacent attached porcine retina compared to the untreated control eye with RD.

E. We tested a number of ROCK inhibitors and found that the Aerie compound 13503 is the most potent at reducing synaptic disjunction, reducing it by 64% after subretinal administration and by 40% after intravitreal administration.

F. Subretinal Y27632 preserved cone terminal structure. RD was associated with flattening of the cone pedicle (ie, loss of its normal pyramidal shape), loss of the synaptic ribbon, and loss of invaginations in the synaptic membrane due to loss of contact with horizontal and bipolar cells. Treatment with Y27632 resulted in preservation of the synaptic ribbon, pyramidal pedicle shape, and invaginations of the synaptic membrane.

V. Blocking synaptic disjunction is correlated with improved rod-specific function, as confirmed by electroretinography (ERG), after retina reattachment.[5]

The extent of scotopic ERG B-wave recovery after 2-hour RD followed by 2-day retinal reattachment was highly correlated with the extent of inhibition of synaptic disjunction.

VI. Hypothesis: Visual outcome after RD (spontaneous or iatrogenic) may be improved with Rho kinase inhibitors. Some clinical implications are as follows:[6]

A. Possible evidence for spreading depolarization with disruption in photoreceptor synaptic circuitry in humans with RD:

RD is associated with visual changes outside the area of the RD. Ng et al (ARVO 2021) showed that in patients with macula-on RD, retinal sensitivity loss extends beyond the RD border toward the fovea. Using the fellow eye as a control, retinal sensitivity loss was 22 dB at 3° inside the RD and decreased approximately linearly to 4 dB at 2° outside the RD. The loss further decreased outside the RD until it reached a plateau of 2 dB at 6°.

B. Visual outcome after RD (eg, near or in the fovea) might be augmented with adjunctive use of ROCK inhibitors in the following settings:

1. Iatrogenic RD: cell or gene delivery to the subretinal space
2. Spontaneous rhegmatogenous RD (macula-on and macula-off)
3. Traction RD from diverse causes (ROP, diabetic retinopathy, proliferative vitreoretinopathy)
4. RD is a model of retinal trauma (?commotio retinae?).

References

1. Erickson PA, Fisher SK, Anderson DH, Stern WH, Borgula GA. Retinal detachment in the cat: the outer nuclear and outer plexiform layers. *Invest Ophthalmol Vis Sci*. 1983; 24(7):927-942.
2. Fisher SK, Lewis GP, Linberg KA, Verardo MR. Cellular remodeling in mammalian retina: results from studies of experimental retinal detachment. *Prog Retin Eye Res*. 2005; 24(3):395-431.
3. Wang J, Zarbin M, Sugino I, Whitehead I, Townes-Anderson E. RhoA signaling and synaptic damage occur within hours in a live pig model of CNS injury, retinal detachment. *Invest Ophthalmol Vis Sci*. 2016; 57(8):3892-3906.
4. Townes-Anderson E, Wang J, Halasz E, et al. Fasudil, a clinically used ROCK inhibitor, stabilizes rod photoreceptor synapses after retinal detachment. *Transl Vis Sci Technol*. 2017; 6(3):22.
5. Halasz E, Zarbin MA, Davidow AL, Frishman LJ, Gombkoto P, Townes-Anderson E. ROCK inhibition reduces morphological and functional damage to rod synapses after retinal injury. *Sci Rep*. 2021; 11(1):692.
6. Halasz E, Townes-Anderson E, Zarbin MA. Improving outcomes in retinal detachment: the potential role of rho-kinase inhibitors. *Curr Opin Ophthalmol*. 2020; 31(3):192-198.

Surgical Videos: Cool Cases and Complications

Subretinal Blu

Grazia Pertile MD

This video is about a complication that occurred injecting Blu dye in a highly myopic eye with a macular hole to stain the internal limiting membrane (ILM). Due to the friction of the syringe plunger, the dye does not come out fluidly. The surgeon increases the pressure on the plunger to promote the injection but, inadvertently, goes deeper into the eye with the needle. All of a sudden, the plunger unlocks. A strong dye jet hits the retina inside the deep staphyloma, penetrates the retina, and ends up underneath. The small retinal hole is treated with laser and gas tamponade.

Unfortunately, the patient comes back 1 month later with a posterior pole detachment and an enlarged hole. As it is situated in the steep part of the staphyloma, there is no way to close it but by plugging it with "something." The ILM was already removed, so we decide to use a retinal patch grafted from the periphery to close it. Fortunately, it did the job: 2 years later the retina is attached and both the macular and the iatrogenic hole are nicely closed.

Suprachoroidal Air

Marcos P Avila MD

Endophthalmitis

Geoffrey G Emerson MD PhD

A 65-year-old man developed endophthalmitis 2 days after cataract surgery and underwent vitreous tap and inject with vancomycin and ceftazidime. Culture showed 4+ *Streptococcus mitis* (pan-sensitive). Two days thereafter, vision worsened from HM to LP, prompting vitrectomy and anterior chamber (AC) washout. Fluffy white material was debulked from the AC and vitreous cavities. The view of the retina was blurry due to edema and inflammatory debris. An air–fluid exchange was performed, the vitreous cavity was filled with silicone oil, and intravitreal antibiotics were repeated. Two weeks later, the surgical view was improved, allowing a more complete vitrectomy and peeling of inflammatory membranes. Retinal detachment, hemorrhages, and whitening were apparent inferiorly. The inferior retina was flattened and lasered, and silicone oil was replaced. The oil was removed 6 months later, and visual acuity stabilized at 20/160.

Due to reduced visibility in the setting of acute endophthalmitis, minimal vitrectomy is appropriate during the initial surgery, to be followed later by more complete surgery when the surgical view is clear.

Endolaser

Gerardo Garcia-Aguirre MD

A routine vitrectomy for vitreous hemorrhage due to proliferative diabetic retinopathy suddenly turns into an intraocular foreign body removal surgery. Predisposing factors that led to this complication and how it was solved will be discussed during the session.

Scleral Buckling and Subretinal Hemorrhage

Maria H Berrocal MD

An 84-year-old pseudophakic woman with a rhegmatogenous detachment was treated with an encircling scleral buckle and vitrectomy. During the suturing of the buckle, a perforation of the sclera was noted. The vitrectomy trochar/cannulas were quickly placed and the infusion started at an IOP of 40 to stop subretinal bleeding. Perfluoron was injected into the vitreous, and sequential movement of the globe was done to displace the blood out of the foveal area. Once the blood was in the periphery, it was aspirated through the pre-existing retinal breaks. Laser was applied to the breaks, and a fluid–air exchange was done. A gas tamponade was performed, and the eye was positioned with the area of the perforation inferiorly to prevent any residual blood from reaching the fovea in the perioperative period.

Financial Disclosure

The Academy has a profound duty to its members, the larger medical community and the public to ensure the integrity of all of its scientific, educational, advocacy and consumer information activities and materials. **Thus each Academy Trustee, Secretary, committee Chair, committee member, taskforce chair, taskforce member, councilor, and representative to other organizations ("Academy Leader"), as well as the Academy staff and those responsible for organizing and presenting CME activities must disclose interactions with Companies and manage conflicts of interest or the appearance of conflicts of interest that affect this integrity. Where such conflicts or perceived conflicts exist, they must be appropriately and fully disclosed and resolved.**

All contributors to Academy educational and leadership activities must disclose all financial relationships (defined below) to the Academy annually. The ACCME requires the Academy to disclose the following to participants prior to the activity:

- All financial relationships with Commercial Companies that contributors and their immediate family have had within the previous 12 months. A commercial company is any entity producing, marketing, re-selling or distributing health care goods or services consumed by, or used on, patients.
- Meeting presenters, authors, contributors or reviewers who report they have no known financial relationships to disclose.

The Academy will request disclosure information from meeting presenters, authors, contributors or reviewers, committee members, Board of Trustees, and others involved in Academy leadership activities ("Contributors") annually. Disclosure information will be kept on file and used during the calendar year in which it was collected for all Academy activities. Updates to the disclosure information file should be made whenever there is a change. At the time of submission of a Journal article or materials for an educational activity or nomination to a leadership position, each Contributor should specifically review his/her statement on file and notify the Academy of any changes to his/her financial disclosures. These requirements apply to relationships that are in place at the time of or were in place 12 months preceding the presentation, publication submission, or nomination to a leadership position. Any financial relationship that may constitute a conflict of interest will be resolved prior to the delivery of the activity.

Visit www.aao.org/about/policies for the Academy's policy on identifying and resolving conflicts of interest.

Financial Relationship Disclosure

For purposes of this disclosure, a known financial relationship is defined as any financial gain or expectancy of financial gain brought to the Contributor or the Contributor's immediate family (defined as spouse, domestic partner, parent, child or spouse of child, or sibling or spouse of sibling of the Contributor) by:

- Direct or indirect compensation;
- Ownership of stock in the producing company;
- Stock options and/or warrants in the producing company, even if they have not been exercised or they are not currently exercisable;
- Financial support or funding to the investigator, including research support from government agencies (e.g., NIH), device manufacturers, and\or pharmaceutical companies; or
- Involvement with any for-profit corporation that is likely to become involved in activities directly impacting the Academy where the Contributor or the Contributor's family is a director or recipient

Description of Financial Interests

Category	Code	Description
Consultant / Advisor	C	Consultant fee, paid advisory boards or fees for attending a meeting
Employee	E	Employed by a commercial company
Lecture Fees	L	Lecture and speakers bureau fees (honoraria), travel fees or reimbursements when speaking at the invitation of a commercial company
Equity Owner	O	Equity ownership/stock options (publicly or privately traded firms, excluding mutual funds)
Patents / Royalty	P	Patents and/or royalties that might be viewed as creating a potential conflict of interest
Grant Support	S	Grant support from all sources

Financial Disclosures

Nisha Acharya MD
None

Anita Agarwal MD
None

Lloyd P Aiello MD PhD
Janssen: S
Kalvista: C,O
Novo Nordisk: C
Regeneron Pharmaceuticals, Inc.: C

Robert L Avery MD
Adverum: C,O
Alcon Laboratories, Inc.: C,O
Alimera Sciences, Inc.: C
Allergan: C
Amgen: C
Apellis: C
Bausch + Lomb: C
Clearside: C
Eyepoint: C,O
Genentech: C,S
InFocus Capital Partners: C,O
Iridex: C
Notal Vision, Inc.: C
Novartis Pharmaceuticals Corp.: C,O
Ocular Theraputix: C
Pr3vent, Inc.: C
Regeneron Pharmaceuticals, Inc.: O,S
RegenXbio: C,S
Replenish: C,O,P
Santen, Inc.: C
Visionary Ventures: C,O

Marcos P Avila MD
None

Carl C Awh MD
Adverum Biotechnolgies: S
Allergan, Inc.: C
Apellis Pharmaceuticals: S
ArcticDx, Inc.: O,P
Bausch + Lomb: C
Genentech: C,S
GlaxoSmithKline: S
Hoffman La Roche, Ltd.: S
Katalyst Surgical, LLC: C,O,P
Kodiak Sciences: S
Merck & Co., Inc.: S
Ophthotec: S
PanOptica: S
Regeneron Pharmaceuticals, Inc.: S
Stealth BioTherapeutics: S

Sophie J Bakri MD
Adverum: C
Alimera: C
Allergan: C
Eyepoint: C
Genentech: C
Kala Pharmaceuticals: C
Novartis, Alcon Pharmaceuticals: C
Roche: C
Zeiss: C

Caroline R Baumal MD
Apellis: C
Carl Zeiss, Inc.: L
Gemini: C
Genentech: C,L
Novartis Pharma AG: C
Regeneron Pharmaceuticals, Inc.: L

Lbachir Benmohamed PhD
None

Audina M Berrocal MD
Aerie: C
AGTC: C
Alcon Laboratories, Inc.: C
Allergan: C
DORC International, bv/Dutch Ophthalmic, USA: C,L
Novartis: C
Oculus Surgical, Inc.: C
Phoenix: C
ProQR: C
Visunex: C
Zeiss: C

Maria H Berrocal MD
Alcon Laboratories, Inc.: C,L
Allergan: C,L
Genentech: C
Oculus Surgical, Inc.: L
Quantel Medical: L

Cagri G Besirli MD
CureVac: C
iRenix Medical: C,O,P
Janssen: C
MeiraGTx: C
ONL Therapeutics: P

Barbara Ann Blodi MD
None

Disclosures current as of 10/29/21. Check the Mobile Meeting Guide for the most up-to-date financial disclosures.

David S Boyer MD
Adverum Biotechnologies: C
Aerie Pharmaceuticals: C
Aerpio: C
Alcon Laboratories, Inc.: C
Alkahest: C
Allegro: C,O
Allergan: C
Allgenesis: C
Appelis: C
AsclepiX Therapeutics: C
Bausch + Lomb: C
Bayer Healthcare Pharmaceuticals: C
Biogen Inc.: C
BioMotiv: C
BioTime, Inc.: C
Boehringer-Ingelheim Pharmaceuticals: C
Cell Cure: C
Chengdu Kanghong Biotech: C
CoDa Therapeutics: C
Daiichi Sankyo Co. Ltd.: C
DigiSight: O
Everads Therapy, Ltd.: C
EyePoint Pharmaceuticals: C
Foresight Biotherapeutics: C
Galimedix Therapeutics: C
Genentech: C
GenSight Biologics: C
Glaukos Corp.: C
GrayBug Vision: C
Iconic Therapeutics: C
Interface Biologics, Inc.: C
Ionis: C
Iveric: C
Kala Pharmaceuticals: C
LumiThera, Inc.: C
Neurotech: C
NGM Biopharma: C
Notal Vision, Inc.: C
Novartis Pharmaceuticals Corp.: C
Novartis, Alcon Pharmaceuticals: C,S
Ocugen, Inc.: C
Ocular Therapeutix: C,S
Ophthotech: C
Opthea: C
Optos, Inc.: C
Optovue: C
Ora, Inc.: C
Orbit Biomedical: C
Oxurion: C
RecensMedical, Inc.: C
Regeneron Pharmaceuticals, Inc.: C
RegenXbio: C
Regulus Therapeutics: C
River Vision: C
Samumed, LLC: C
Santen, Inc.: C
SciFluor: C
Semathera: C
Shire: C
Stealth BioTherapeutics: C
Sun Pharmaceutical Industries: C
Taiwan Liposomal Company: C
Thea: C
ThromboGenics: C

Neil M Bressler MD
Bayer Healthcare Pharmaceuticals: S
Biogen, Inc.: S
Novartis Pharmaceuticals Corp.: S
Regeneron Pharmaceuticals, Inc.: S
Roche: S
Samsung Bioepis: S

Susan B Bressler MD
Amgen: C
Bayer Healthcare Pharmaceuticals: S
Biocon: S
Biogen, Inc.: S
Boehringher Ingleheim: S
Eye Point: S
Genentech: S
Mylan: S
Notal Vision, Inc.: S
Novartis, Alcon Pharmaceuticals: S
Regeneron Pharmaceuticals, Inc.: S

David M Brown MD
Adverum: C
Allegro: C,S
Allergan: C,S
Annexon: C
Apellis: C,S
Astellas: S
Avalanche/Adverum: S
Boehringer Ingelheim: C,S
Carl Zeiss, Inc.: C
Clearside: C,S
Genentech: C,S
Heidelberg Engineering: C
Iconic: S
Janssen: C
Johnson & Johnson: C
Kanghong Pharma: C
National Eye Institute: S
Notal Vision, Inc.: C
Novartis, Alcon Pharmaceuticals: C,S
Ohr: C,S
Ophthotech: C,S
Opthea: S
Optos, Inc.: C,P
Optovue, Inc.: C
Pfizer, Inc.: C
PRN Physician Recommended Nutriceuticals: S
Regeneron Pharmaceuticals, Inc.: C,S
Regenix Bio: C,S
Samsung Bioepsis: C,S
Samsung: C,S
Santen: C,S
SciFlour Life Sciences: S
Second Sight Medical Products, Inc.: S
Senju Pharmaceutical Co., Ltd.: C
Stealth Biotherapeutics: C
Taiwan Liposome: S
ThromboGenics, Inc.: C,S
Tyrogenix: C,S
Vinci: C

Peter A Campochiaro MD
Aerpio: C,S
Allegro: C,O
Allergan: C,S
AsclipiX: C,S
Ashvattha Therapeutics: C,S
Bausch + Lomb: C
Clearside: C
CureVac: C
Exonate: C
Genentech: C,S
Genzyme: S
Graybug: C,O,P,S
Intrexon: C
Mallinckrodt Pharmaceuticals: S
Merck & Co., Inc.: C
Novartis, Alcon Pharmaceuticals: C
Oxford BioMedica: S
Perfuse: C
Regeneron: C,S
RegenXbio: S
Roche: C,S
Wave Life Sciences: C

Antonio Capone Jr MD
Aura Biosciences: S
Broadspot: O
Caeregen Therapeutics: O,P
Genentech: S
Ionis Pharmaceuticals, Inc.: S
Novartis Pharmaceuticals Corp.: S
Phoenix Technology Group: O
ProQR Therapeutics: C
Regeneron Pharmaceuticals, Inc.: S
Spark Therapeutics: C

Usha Chakravarthy MBBS PhD
Roche Diagnostics: C

R V Paul Chan MD
Alcon Laboratories, Inc.: C
National Institutes of Health: S
Phoenix Technology Group: C

Jonathan Chang MD
None

Stanley Chang MD
Alcon Laboratories, Inc.: L
Genentech: C
Lowy Medical Foundation: C

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

Emily Y Chew MD
None

Michael F Chiang MD
Genentech: S
Inteleretina: O
National Eye Institute: S
National Science Foundation: S
Novartis Pharmaceuticals Corp.: C

Netan Choudhry MD
Allergan: C,L
Bayer: C,L,S
Ellex: L
Hoffman La Roche, Ltd.: C
Johnson & Johnson: L
Optos: C,L
Topcon: C,L
Zeiss: C,S

David R Chow MD
Alcon Laboratories, Inc.: C
Allergan: C
Bayer Healthcare Pharmaceuticals: C,L
DORC International, bv/Dutch Ophthalmic, USA: C,L
Katalyst: C,P
Novartis, Alcon Pharmaceuticals: C,L
Optovue: L
Roche Diagnostics: C

Karl G Csaky MD
AbbVie: C
Adverum Biotechnologies: C
Allergan: C
Genentech/Roche: C
Gyroscope: C
Heidelberg Engineering: C
Johnson & Johnson: C
Merck & Co., Inc.: C
NGM Biopharmaceuticals: C
Novartis Pharma AG: C
Ocular Therapeutix: C
Retrotope: C
Ribomic: C

Donald J D'Amico MD
Alcon Laboratories, Inc.: C
Iveric Bio, Inc.: C,O

Vaidehi Shradha Dedania MD
Alimera Sciences, Inc.: C
Allergan, Inc.: C
Clover Therapeutics: C
Novartis Pharma AG: C
Regeneron Pharmaceuticals, Inc.: C

Dilsher S Dhoot MD
Alimera Sciences, Inc.: C
Allergan: C
Bayer Healthcare Pharmaceuticals: C
EyePoint Pharmaceuticals: C
GENENTECH: C
Novartis, Alcon Pharmaceuticals: C
Optos, Inc.: C
Regeneron: C
Santen, Inc.: C

Diana V Do MD
Bayer Healthcare Pharmaceuticals: C
Boerhinger Ingelheim: C,S
Eyepoint: C
Kodiak Sciences: C,O
Mallinckrodt Pharmaceuticals: C
Novartis Pharma AG: C,S
Regeneron Pharmaceuticals, Inc.: C,S
Santen, Inc.: C,S

Jay S Duker MD
Aura Bio: C
Carl Zeiss Meditec: S
EyePoint Pharma: E
Hoffman La Roche, Ltd.: C
Novartis, Alcon Pharmaceuticals: C
OptoVue: S
Sesen Bio: C

Jacque L Duncan MD
AbbVie: S
Acucela: S
AGTC: C
Biogen Inc.: S
Editas: C
Eyevensys: C
Foundation Fighting Blindness: S
Gyroscope: C
National Eye Institute: S
SparingVision: C
Spark Therapeutics, Inc.: C
Vedere Bio: C

Justis P Ehlers MD
Adverum: C
Aerpio: C,S
Alcon Laboratories, Inc.: C,S
Allegro: C
Allergan: C
Bioptigen: C,P
Carl Zeiss Meditec: C
Genentech: C,S
Leica: C,P
National Eye Institute: S
Novartis Pharma AG: C,S
Regeneron Pharmaceuticals, Inc.: C,S
Santen, Inc.: C
Stealth: C
Thrombogenics: C,S

David A Eichenbaum MD
Alimera Sciences, Inc.: C
Alkahest: S
Allergan: C,L,S
Apellis: C
AsclepiX: S
Bayer: S
Boston Image Reading Center: O
Chengdu: S
Clearside: O,S
DORC International, bv/Dutch Ophthalmic, USA: C
Gemini Therapeutics: S
GENENTECH: C,L,S
Gyroscope: C,S
Hemera Biosciences: O
KKR: C
Mylan: S
Network Eye: O
NGM: S
Notal Vision, Inc.: C,L
Novartis, Alcon Pharmaceuticals: C,S
Ophthotech: S
RecensMedical: C
Regeneron Pharmaceuticals, Inc.: C,S
US Retina: O

Dean Eliott MD
Alcon: C
Aldeyra Therapeutics: C,O,P
Allergan: C
DORC: C
Genentech: C
Glaukos Corp.: C
Neurotech: S
Pykus Therapeutics: C,O

Geoffrey G Emerson MD PhD
DaVita, Inc.: O
Gilead Sciences: O
Glaukos Corp.: O
Novartis Pharma AG: O
Ocular Therapeutix: O
Pfizer, Inc.: O
Regeneron Pharmaceuticals, Inc.: O
Regenxbio, Inc.: O
Santen, Inc.: O

Nicole Eter MD
Allergan: C,L
Bayer Healthcare Pharmaceuticals: C,L,S
Novartis Pharmaceuticals Corp.: C,L,S
Roche: C,L

Amani Fawzi MD
Boehringer Ingelheim: C
National Institute of Health: S
Regeneron Pharmaceuticals, Inc.: C
Roche, Inc.: C

Harry W Flynn Jr MD
None

Jasmine H Francis MD
None

K Bailey Freund MD
Allergan: C
Bayer Healthcare Pharmaceuticals: C
Genentech/Roche: S
Heidelberg Engineering: C
Novartis, Alcon Pharmaceuticals: C
Regeneron Pharmaceuticals, Inc.: C
Zeiss: C

Gerardo Garcia-Aguirre MD
Alcon Laboratories, Inc.: C,L
Allergan: C,L
Bayer Pharmaceuticals: C,L
Genentech: L
Heidelberg Engineering: L
Nidek, Inc.: L
Novartis Pharma AG: C,L
Zeiss: L

Sunir J Garg MD FACS
Allergan, Inc.: S
Apellis: S
Bausch + Lomb: C
Boehringer Ingelheim: C,S
Johnson & Johnson: C
Nexttech: O
NGM Bio: S
Regeneron Pharmaceuticals, Inc.: S

Alain Gaudric MD
None

Mark C Gillies MD PhD
Allergan: C,L,S
Bayer Healthcare Pharmaceuticals: C,L,S
Novartis Pharmaceuticals Corp.: C,L,S
Roche Diagnostics: C

Roger A Goldberg MD
Aerie Pharmaceuticals, Inc.: S
Allergan: C,L
Apellis: S
Carl Zeiss Meditec: C,L,S
Emmetrope Ophthalmics: O
GENENTECH: C,L,S
Graybug: S
Novartis Pharma AG: S
Regeneron Pharmaceuticals, Inc.: C

Justin Gottlieb MD
None

Evangelos S Gragoudas MD
Astellas Institute for Regenerative Medicine: C
Aura Pharmaceuticals: C
Valeant: P

Dilraj Singh Grewal MD
Allergan: C
Eyepoint: C
Iveric Bio: C

Robyn H Guymer MBBS PhD
Apellis: C
Bayer Healthcare Pharmaceuticals: C
Genentech: C
Hoffman La Roche, Ltd.: C
Novartis Pharma AG: C

Paul Hahn MD PhD
Alimera Sciences, Inc.: C
DORC International, bv/Dutch Ophthalmic, USA: C
Genentech: C,L

Julia A Haller MD
Aura Biosciences: C
Bionic Sight LLC: C
Bristol Myers Squibb: O
Eyenovia: O
KalVista: C
Lowy Medical Research Institute: C
Novartis Pharmaceuticals Corp.: C
Opthea: O

J William Harbour MD
Castle Biosciences, Inc.: C,P

Tarek S Hassan MD
Alcon Laboratories, Inc.: C
Allergan: C
ArcticDx, Inc.: C,O
Aviceda: C,O
Bayer Healthcare Pharmaceuticals: C
Beaver-Visitec International, Inc.: C
Broadspot: O
Genentech: C
Hoffman La Roche, Ltd.: C
Iveric Bio: C
Katalyst Surgical, LLC: C,P
Novartis Pharmaceuticals Corp.: C
Oculus Surgical, Inc.: C,P
Ocutrx: C
Regeneron Pharmaceuticals, Inc.: C
Surgicube: C
Vitreq: C

Jeffrey S Heier MD
4DMT: C
BVT: C
Galimedix: C
Abpro: C
Adverum: C
Aerie: C
Affamed: C
Allegro: C
Allergan: C
Allgenesis: C
Annexon: C
Apellis: C,S
Aprea: C
Asclepix: C,S
Aviceda: C
Bayer: S
DTx: C
Eloxx: C
Genentech/Roche: C,S
Graybug: C
Gyroscope: C,S
Hemera: S
Horizon Therapeutics: C
Iveric: C,S
Kanghong: C,S
Kodiak: S
Lensgen: C
NGM: C,S
Notal Vision: S
Novartis: C,S
Ocular Therapeutix: C
Oriole: C
Oxurion: C
Palatin: C
Regeneron: C,S
Regenxbio: C,S
Roche: C
Santen: C
Scifluor: C
Stealth Biotherapeutics: C,S
Surrozen: C
Thea: C
Verseon: C
Vinci: C

Allen C Ho MD
Aerpio: C,S
AGTC: C,S
Alcon Laboratories, Inc.: C,S
Allergan: C,S
Apellis: S
Asclepix: C
Beaver-Visitec International, Inc.: C
Chengdu Kanghong Biotechnology: C,S
Clearside Biomedical: C,S
Covalent Medical, LLC.: O
Genentech: C,S
Iconic: C,S
Iridex: C,S
Johnson & Johnson: C,S
Lineage/BioTime: C
National Eye Institute: S
ONL: C,O
Ophthotech: S
Optovue, Inc.: C,S
PanOptica: C,O
ProQR: C
Regeneron Pharmaceuticals, Inc.: C,S
RegenXbio: C,S
Second Sight Medical Products, Inc.: C,S
Tyrogenix: C

Suber S Huang MD MBA
Diopsys: C,L,S
Lumoptic: C,O
Outlook Therapeutics: C
Regenerative Patch Technologies: C
RegenXbio: C
Second Sight Medical Products: C
Volk Optical, Inc.: C,L
Washington University (St. Louis) DOLF study: C

G Baker Hubbard MD
National Eye Institute: S

Jean-Pierre Hubschman MD
Alcon: C
Allergan: C
Bausch + Lomb: C
UCLA: P
Zeiss: C

Mark S Humayun MD PhD
Alcon Laboratories, Inc.: C,L
Duke Eye Center: P
Golden Eye: C,O,P
Intellimicro (GEB): C,O,P
Iridex: P
John Hopkins University: P
Lutronic Vision: C,O,P
Outlook Therapeutics: C,O
Regenerative Patch Technologies (RPT): C,O,P
Replenish: C,O,P
Second Sight Medical Products, Inc.: P
University of Southern California: E,P

Deeba Husain MD
Allergan, Inc.: C
Genentech: C,S
Lions International Foundation: S
Macula Society/Regeneron: S
National Eye Institute/NIH: S
Omeicos Therapeutics: C

Michael S Ip MD
Alimera: C
Allergan, Inc.: C
Amgen: C
BioTime, Inc.: C
Cell Lineage Therapeutics: C
Clearside: C
Genentech: C
Novartis Pharma AG: C
Occurx: C
Regeneron Pharmaceuticals, Inc.: C
RegenXbio: C

Douglas A Jabs MD MBA
None

Glenn J Jaffe MD
Adverum: C
EyePoint: C
Gemini: C
Hoffman La Roche, Ltd.: C
Iveric: C
Neurotech: C
Novartis Pharma AG: C

Lee M Jampol MD
National Eye Institute: S

Kanishka T Jayasundera MD
None

Mark W Johnson MD
Amgen: C
Apellis: S
Aura Biosciences: C
Pfizer, Inc.: C

J Michael Jumper MD
Allergan: S
Carl Zeiss Meditec: S
Chengdu Kanghong Pharmaceutical Group: S
Covalent Medical LLC: O
DORC International, bv/Dutch Ophthalmic, USA: L
EMD Serono: S
Genentech: S
Graybug Vision, Inc.: S
Kodiak Sciences, Inc.: S
Novartis Pharma AG: S
Topcon Medical Systems, Inc.: S

Peter K Kaiser MD
Aerie: C
Aerpio: C
Allegro: C
Allergan: C
Bayer Healthcare Pharmaceuticals: C,L
Biogen, Inc.: C
Boerenger: C
Clearside: C
Eyevensys: C
Formycon: C
Galecto: C
Galimedix: C
Glaukos: C
iRenix: C
Iveric Bio: C,O
jCyte: C
Kala: C
Kanghong: C
Kodiak: C
Novartis Pharmaceuticals Corp.: C,L
Omeros: C
Opthea: C
Oxurion: C
Regeneron Pharmaceuticals, Inc.: C,L
RegenXBio: C
Retinal Sciences: C,O
Santen: C
Stealth: C
Verana: O

Richard S Kaiser MD
None

Pearse A Keane MBBCh
Allergan, Inc.: L
Apellis: C
Bayer Healthcare Pharmaceuticals: C,L
Big Picture Eye Health: O
BitFount: C
DeepMind Technologies: C
Heidelberg Engineering: L,S
Novartis Pharma AG: C,L
Roche Diagnostics: C,L
Topcon Medical Systems Inc.: C,L

Arshad M Khanani MD
Adverum: C,S
Alkahest: S
Allegro: C,S
Allergan: C,L,S
Gemini: C,S
GENENTECH: C,S
Glaukos: C
Graybug: S,C
Gyroscope: C,S
IVERIC BIO: C,S
KATO: C
Kodiak Sciences: C,S
Neurotech: S
NGM Pharmaceuticals: S
Novartis Pharmaceuticals Corporation: C,L,S
Opthea: C,S
Oxurion (formerly ThromboGenics): C,S
Polyphotonix: C
Recens Medical: C,S
Regenxbio: C,S

Ivana K Kim MD
Allergan, Inc.: S
Biophytis: C
Castle Biosciences: C
Kodiak Sciences: C
Novartis: C

Judy E Kim MD
Adverum: C
Allergan: C
Astellas: C
Gemini: C
Genentech: C
Notal Vision, Inc.: S
Novartis: C
Optos, Inc.: S
Regeneron: C

Stephen J Kim MD
None

Shoji Kishi MD PhD
None

Gregg T Kokame MD
Bausch + Lomb: C
Bayer Healthcare Pharmaceuticals: C
Genentech: S
Iveric: S
Novartis: S
Regeneron Pharmaceuticals, Inc.: C,S
Roche: C
Salutaris: S
Zeiss: C

Baruch D Kuppermann MD PhD
Allegro: C,O,S
Allergan: C,L,S
Apellis: S
Aprea Therapeutics, Inc.: C
Cell Care: C,O
Eyedaptic: C,O
Genentech, Inc.: C,S
Glaukos Corp.: C
Interface Biologics: C
Ionis: S
Iveric Bio: C
jCyte: C,O
Novartis Pharmaceuticals Corp.: C,S
Ocunex Therapeutics: C,O
Regeneron Pharmaceuticals, Inc.: C,S
ReVana Therapeutics: C,O
Ripple Therapeutics: C
Theravance Biopharma: C

Eleonora G Lad MD PhD
Alexion: C
Annexon: C
Apellis: C
Boehringer Ingelheim: S
Galimedix: C
Hoffman La Roche, Ltd.: C,S
Iveric Bio: C
Novartis, Alcon Pharmaceuticals: S
Retrotope: C

David R Lally MD
Aldeyra Therapeutics: S
Alimera Sciences, Inc.: C,L
Allergan, Inc.: C,L
Apellis: C,L,S
Chengdu Kanghong: S
eyepoint: C,S
GENENTECH: C,S
Iveric Bio: S,C
Kodiak Sciences: S
Mac Tel Project: S
Neurotech: S
Notal Vision, Inc.: S
Novartis Pharma AG: C,L,S
Opthea: S
Optos: S
Ora Inc: S
Stealth biotherapeutics: S,L

Aaron Y Lee MD
Carl Zeiss Meditec: S
Food and Drug Administration: E
Genentech: C
Gyroscope: C
Johnson & Johnson Vision: C
Microsoft: S
Nvidia: S
Santen, Inc.: S
Verana Health: C

Gareth M Lema MD PhD
None

Theodore Leng MD
Astellas: S
Boehringer Ingelheim: C
Genentech: C
Kodiak: S
Regeneron Pharmaceuticals, Inc.: C
Targeted Therapy Technologies: S
Verana Health: C

Jennifer Irene Lim MD
Aldeyra Therapeutics: S
Allergan, Inc.: C
Aura Biosciences: C
Chengdu Kanghong: S
Cognition Therapeutics: C
CRC Press/Taylor and Francis: P
Eyenuk: C
Genentech: C,S
Greybug: S
Iveric Bio: C
JAMA Ophthalmology Editorial Board: C
Luxa: C
NGM: S
Novartis Pharma AG: C
Ophthea: C
Quark: C
Regeneron Pharmaceuticals, Inc.: S,C
Santen, Inc.: C
Stealth: S
Unity: C
Viridian: C

Phoebe Lin MD PhD
None

Anat Loewenstein MD
Allergan: C
Bayer Healthcare Pharmaceuticals: C
Beyeonics Surgical, Ltd.: C
Notal Vision, Inc.: C,S
Novartis Pharmaceuticals Corp.: C,S
Roche: C
WebMD: C

Mathew W MacCumber MD PhD
Allergan, Inc.: C
Apellis: S
Cardinal Health: C
Clearside Biomedical, Inc.: C
Covalent Medical: O
Genentech: C
National Eye Institute: S
Novartis Pharma AG: C
Regeneron: C
Spark Therapeutics: C
US Retina: O,C

Daniel F Martin MD
None

Raj K Maturi MD
Aiviva: C
Boehringer-Ingelheim: S
DORC: C
Eli Lilly: S
ForwardVue: O
Gemini Therapeutics: S
Genentech: S
Neurotech: C
NGM Biopharmaceuticals, Inc.: S
Oculinea: O
Oxurion: C
Regenxbio: S
Ribomic: S
Samsung: S
Santen: S
Unity Biotechnology: S

Colin A McCannel MD
DORC International, bv/Dutch Ophthalmic, USA: C,L
Genentech: S

Tara A McCannel MD
None

H Richard McDonald MD
None

Carsten H Meyer MD
None

William F Mieler MD
None

Prithvi Mruthyunjaya MD
Alcon Laboratories, Inc.: C
Aura: C
Castle Biosciences, Inc.: C

Timothy G Murray MD MBA
Alcon Laboratories, Inc.: C
FDA: C

Quan Dong Nguyen MD
Bausch + Lomb: C
Eyegate Pharmaceuticals, Inc.: C
Genentech: C
Regeneron Pharmaceuticals, Inc.: C
Santen, Inc.: C

Kyoko Ohno-Matsui MD
Cooper Vision: C
Santen, Inc.: C

Timothy W Olsen MD
iMacular Regeneration LLC: O
National Eye Institute: S
Novartis Institutes for BioMedical Research, Inc.: S

Susanna S Park MD PhD
Allergan: S
Roche: S

David W Parke II MD
OMIC-Ophthalmic Mutual Insurance Company: C

Barbara Parolini MD
None

Grazia Pertile MD
None

Dante Pieramici MD
Adverum: C,S
Apellis: S
Gemini: C,S
Genentech: C,S
Greybug: S
Ionis: S
Kodiac: S
NGM: S
Novartis Pharma AG: C,S
Ophthea: S
Regeneron Pharmaceuticals, Inc.: C,S
RegenXbio: C,S
Stealth: S

John S Pollack MD
Aldeyra: S
Covalent Medical: O
jCyte: E,O
Notal Vision, Inc.: O
Vestrum Health: O

Jonathan L Prenner MD
Alcon Laboratories, Inc.: C
Allergan, Inc.: C
Carl Zeiss Meditec: C
Novartis Pharma AG: C
Regeneron Pharmaceuticals, Inc.: C

Rajesh C Rao MD
Barbara Dunn Research Fund: S
Beatrice & Reymont Paul Foundation: S
E Matilda Ziegler Foundation for the Blind: S
Elaine Sandman Research Fund: S
Grossman Research Fund: S
Leonard G Miller Ophthalmic Research Fund at the Kellogg Eye Center: S
March Hoops to Beat Blindness: S
National Cancer Institute: S
National Eye Institute: S
Research to Prevent Blindness: S
Roz Greenspon Research Fund: S

Carl D Regillo MD FACS
Adverum: C,S
Alcon Laboratories, Inc.: C,S
Allergan: C,S
Genentech: C,S
Iveric: C,S,O
Kodiak: C,S
Merck & Co., Inc.: C
Notal Vision, Inc.: C,S
Novartis Pharmaceuticals Corp.: C,S
Regeneron Pharmaceuticals, Inc.: S
Regenxbio: S
Takeda: C

Kourous Rezaei MD
Alcon Laboratories, Inc.: C
BMC: C
Iveric Bio: O,C

Richard B Rosen MD
Astellas: C
Boehringer Ingelheim: C
CellView: C
Genentech: S
Guardion Health: C,O
Nano Retina: C
OD-OS: C
Opticology: O
Optovue: C,P
Regeneron Pharmaceuticals, Inc.: C
Teva: C

Philip J Rosenfeld MD PhD
Apellis: C,O
Bayer Healthcare Pharmaceuticals: C
Boehringer-Ingelheim: C
Carl Zeiss Meditec: C,S
Chengdu Kanghong Biotech: C
Iveric Bio: S
Ocudyne: C,O
Ocunexus: C
Regeneron Pharmaceuticals, Inc.: C
Stealth Biotechnology: S
Unity Biotechnology: C
Valitor, Inc.: C
Verana Health: O

Srinivas R Sadda MD
4DMT: C
Allergan: C
Amgen: C
Apellis: C
Astellas: C
Bayer Healthcare Pharmaceuticals: C
Carl Zeiss Meditec: C,L,S
Centervue: C
Genentech: C
Heidelberg Engineering: C,L,S
Iveric Bio: C
Merck & Co., Inc.: C
Nidek: L
Novartis Pharma AG: C,L
Optos, Inc.: C
Oxurion: C
Regeneron Pharmaceuticals, Inc.: C
Topcon Medical Systems Inc.: L

Jose A Sahel MD
Chronolife: O
GenSight Biologics: P,O,C
IHU FOReSIGHT (ANR-18-IAHU-01): S
LabEx LIFESENSES (ANR-10-LABX-65): S
NewSight: C,O
Pixium Vision: C,O
Prophesee: O
Sparing Vision: P,O,C
Tilak Healthcare: C,O
Vegavect: C,O

David Sarraf MD
Amgen: C,S
Bayer Healthcare Pharmaceuticals: C,L
Boehringer Inc: S
Genentech: C,S
Heidelberg Engineering: S
Iveric Bio: C
Novartis Pharmaceuticals Corp.: C,L
Optovue: C,L,S
Regeneron Pharmaceuticals, Inc.: S
Topcon Medical Systems, Inc.: S

Shlomit Schaal MD PhD
None

Ursula M Schmidt-Erfurth MD
Boehringer: C
Genentech: C,S
Kodiak: S
Novartis Pharma AG: C,S
RetInSight: C
Roche Diagnostics: C

Steven D Schwartz MD
Astellas: S
Broad Center for Regenerative Medicine, UCLA: S
California Institute of Regenerative Medicine: S
Nikon: S
University of California at Los Angeles: E
Verana Health: O

Adrienne Williams Scott MD
Allergan: C
GENENTECH: C
Novartis Pharma AG: C
Regeneron Pharmaceuticals, Inc.: C

J Sebag MD FACS FRCOphth FARVO
Alcon Laboratories, Inc.: C

Gaurav K Shah MD
Allergan, Inc.: C,L,S
DORC International: S
OMIC-Ophthalmic Mutual Insurance Company: C
Regeneron Pharmaceuticals, Inc.: C,L,S

Veeral Sheth MD
Alimera Sciences, Inc.: C,S
Allergan, Inc.: S
Chengdu Kanghong: S
DRCR: S
EyePoint: C
GENENTECH: C,L,S
Gyroscope: S
Ionis: S
IvericBio: S
NGM Biopharmaceuticals: S
Novartis Pharma AG: C,S
Regeneron Pharmaceuticals, Inc.: S
SalutarisMD,: S
SamChungDang: S
Santen, Inc.: S

Paul A Sieving MD PhD
Newsight Therapeutics, Inc.: O
VegaVect, Inc.: O

Michael A Singer MD
Aerpio: C,S
Aestelis: S
Alimera Sciences, Inc.: S
Allergan: C,L,S
Ampio: C,L,S
Clearside: C,S
Genentech: C,L,S
Guidepoint: C
Kodiak: C
Mallinckrodt Pharmaceuticals: L
Novartis Pharma AG: C,S
Optos, Inc.: S
pSivida: C
Regeneron Pharmaceuticals, Inc.: L,S
Santen, Inc.: C
Spark Therapeutics, Inc.: C

Lawrence J Singerman MD
Alimera Sciences, Inc.: E,S
Alkeus: S
Apellis: S
Chengdu: S
Genentech: S
Kodiak Pharmaceuticals: S
National Eye Institute: S
Novartis Pharmaceuticals: S
Oxurion: S
Roche: S

Rishi P Singh MD
Alcon Laboratories, Inc.: C
Apellis: S,C
Bausch + Lomb: C
Genentech: C
Gyroscope: C
Novartis: C
Regeneron Pharmaceuticals, Inc.: C
Zeiss: C

Elliott H Sohn MD
Oxford Biomedica: S

Sharon D Solomon MD
None

Richard F Spaide MD
Bayer Healthcare Pharmaceuticals: C
DORC International, bv/Dutch Ophthalmic, USA: P
Genentech: C
Heidelberg Engineering: C
Regeneron Pharmaceuticals, Inc.: C
Roche Diagnostics: C
Topcon Medical Systems, Inc.: C,P

Sunil K Srivastava MD
Allergan: C,S
Bausch + Lomb: C,S
Carl Zeiss, Inc.: C
Clearside: C
Gilead Sciences: C
Novartis Pharma AG: C
Novartis, Alcon Pharmaceuticals: C
Optos, Inc.: C
pSividia: C
Regeneron Pharmaceuticals, Inc.: C
Santen, Inc.: C,S

Peter W Stalmans MD PhD
Carl Zeiss Meditec: C,S
DORC International, bv/Dutch Ophthalmic, USA: C
Nano-Retina: C
Vitreq B.V.: C

Paulo E Stanga MD
Apellis: C,S
Canon Medical Systems Europe: C,S
Carl Zeiss Meditec AG: C,L,S
Celltrion: C
Gyroscope Therapeutics Limited: C,S
Imagine Eyes: C,S
IvericBio: C,S
Keeler Instruments, Inc.: C,S
Lumithera: C,S
Maculogix: S
Optos plc: C,L,S
Quantel Medical: C,S

Giovanni Staurenghi MD
AbbVie: C
Apellis: C
Astellas: C
Bayer Healthcare Pharmaceuticals: C
Boheringer: C
Carl Zeiss Meditec: L,S
Centervue: C,L,S
Chengdu Kanghong Biotechnology: C
Genentech: C
Heidelberg Engineering: C,L,S
Hoffman La Roche, Ltd.: C,L,S
Iveric: C
Kyoto Drug Discovery & Development Co.: C
Nidek, Inc.: L,S
Novartis Pharmaceuticals Corp.: C,L,S
Ocular Instruments, Inc.: P
Optos, Inc.: C,S
Optovue, Inc.: S
Quantel Medical: S

Paul Sternberg Jr MD
Diabetic Retinopathy Clinical Research Network: C
International Retinal Research Foundation: C

Jennifer K Sun MD
Adaptive Sensory Technology: S
Genentech: S
JAMA Ophthalmology: E
Novartis Pharma AG: S
Novo Nordisk: C,S
Optovue: S
Roche: C,S

Ramin Tadayoni MD PhD
Alcon Laboratories, Inc.: C
Allergan: C
Apellis: C
Bausch + Lomb: C
Bayer Healthcare Pharmaceuticals: C
Carl Zeiss Meditec: C
Chibret International: C
Genentech: C
Hoffman La Roche, Ltd.: C
Iveric Bio: C
KHB: C
Moria: C
Novartis, Alcon Pharmaceuticals: C
Oculis: C
ThromboGenics, Inc.: C

John T Thompson MD
EHR Command Center, LLC: O
Genentech: S
Ocutrx Vision Technologies, LLC: O

Nadia Khalida Waheed MD
Alkahest: C
Bayer Healthcare Pharmaceuticals: S
Carl Zeiss Meditec: C,S
Genentech: C
Gyroscope: E,O
Heidelberg Engineering: C
Nidek, Inc.: S,C
Ocudyne: O
Regeneron Pharmaceuticals, Inc.: C,S
Topcon Medical Systems Inc.: C

John A Wells III MD
Adverum: C,S
Genentech: C,S
Iveric: S
Jaeb Center for Health Research: C,S
Kodiak: S
National Eye Institute: S
Neurotech: S
Optos, Inc.: S
Regeneron : S

Christina Y Weng MD MBA
Alcon Laboratories, Inc.: C
Alimera Sciences, Inc.: C
Allergan: C
DORC International, bv/Dutch Ophthalmic, USA: C
Genentech: C
Novartis Pharma AG: C
Regeneron Pharmaceuticals, Inc.: C
RegenXbio: C

George A Williams MD
None

Sebastian Wolf MD PhD
Bayer Healthcare Pharmaceuticals: C,S
Carl Zeiss Meditec: C,S
Chengdu Kanghong Biotechnology: C
European Society of Retina Specialists (EURETINA): C
Heidelberg Engineering: C,S
Novartis Pharmaceuticals Corp.: C,S
RetinAI: C
Roche: C,S

Tien Yin Wong MBBS
Allergan Singapore Pte Ltd.: C,L
Allergan, Inc.: C,L
Bayer Healthcare Co. Ltd.: C,L,S
Bayer Healthcare Pharmaceuticals. Inc.: C,L,S
Boehringer-Ingelheim: C
Eden Ophthalmic: C
EyRIS Pte Ltd.: O
Genentech: C,L,S
Iveric Bio: C
Merck & Co., Inc.: C
Novartis Pharma AG: C,L,S
Oxurion NV: C
Plano Pte Ltd.: O
Roche Diagnostics: C,L,S
Samsung Bioepis: C,L
Shanghai Henlius: C
Zhaoke Pharmaceutical: C

Charles C Wykoff MD PhD
Abbvie C
Adverum Biotechnologies C,S
Aerie Pharmaceuticals, Inc. C,S
Aldeyra S
Alimera Sciences, Inc. S
Alkahest S
Allergan C,S
Allgenesis C
Alnylam C
Amgen S
Annexon C,S
Apellis Pharmaceuticals C,S
Arrowhead C
Asclepix S
Bausch + Lomb C
Bayer Healthcare Pharmaceuticals C,S
Bionic Vision Technologies C
Boehringer Ingelheim S
Chengdu Kanghong C,S
Clearside Biomedical, Inc C,S
EyePoint C
Gemini Therapeutics S
GENENTECH C,S
Graybug Vision S
Gyroscope C,S
IONIS Pharmaceuticals S
iRENIX S
Iveric Bio (formerly Ophthotech) C,S
Janssen C
Kato Pharmaceuticals C
Kodiak Sciences C,S
LMRI S
Long Bridge Medical C
Nanoscope S
Neurotech S
NGM Biopharmaceuticals C,S
Novartis Pharmaceuticals Corporation C,S
OccuRx C
Ocular Therapeutix C
ONL Therapeutic C,O
Opthea C,S
Oxurion S
Palatin C
Perfuse Therapeutics C
PolyPhotonix C,O
RecensMedical C,O,S
Regeneron Pharmaceuticals, Inc. C,S
Regenxbio C,S
Roche C,S
SamChunDang Pharm S
Surrozen C
Taiwan Liposome Company S
Takeda C
Valo Health C
Verana Health C
Visgenx O
Vitranu C
Xbrane Biopharma S

Glenn C Yiu MD PhD
Alimera Sciences, Inc.: C
Allergan: C
Carl Zeiss Meditec: L
Clearside Biomedical: S
Genentech: C
Gyroscope Therapeutics: C
Intergalactic Therapeutics: C
Iridex: L,S
Regeneron Pharmaceuticals, Inc.: C
Topcon Medical Systems Inc.: C
Verily: C

Yoshihiro Yonekawa MD
Alcon Laboratories, Inc.: C

David N Zacks MD PhD
ONL Therapeutics: C,O,P

Marco A Zarbin MD PhD FACS
Aerie Pharmaceuticals, Inc.: S
Boerhinger Ingelheim: C
Cell Cure: C
Chengdu Kanghong Biotechnology: C
Coherus Biosciences: C
Daiichi Sankyo: C
Frequency Therapeutics: C,O
Genentech: C
Hoffman La Roche, Ltd.: C
Iduna Therapeutics: C
Iveric Bio: C,O
Life Biosciences: C
Novartis, Alcon Pharmaceuticals: C,L
NVasc: O
Ophthotech Corp.: C
Perfuse Therapeutics: C
Rutgers University: P
Selphagy: C

Presenter Index

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