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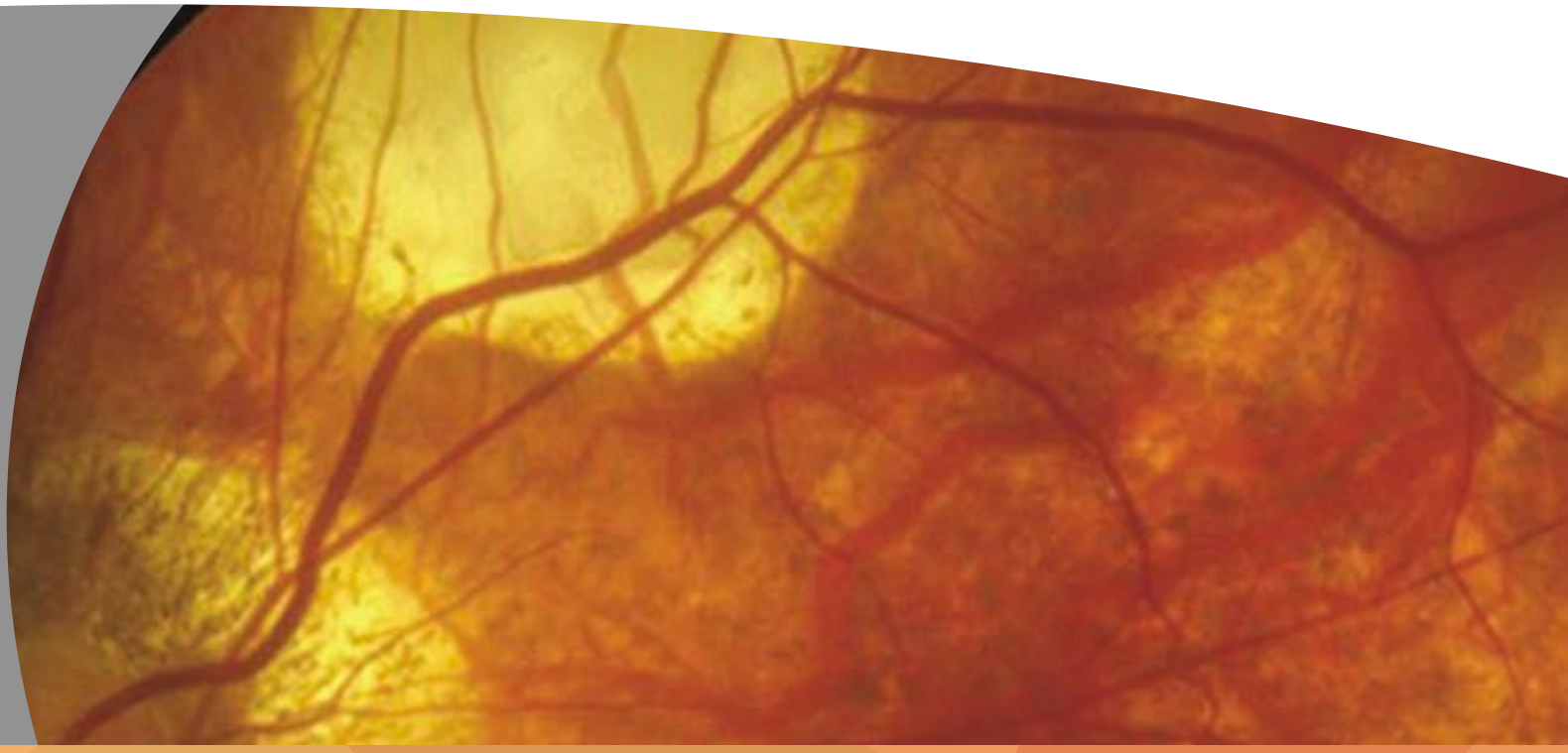

Retina 2022

Retina Reimagined

Subspecialty Day | AAO 2022

Chicago | Sept 30 – Oct 1

Protecting Sight. Empowering Lives.®

Retina 2022
Retina Reimagined

Program Directors
Srinivas R Sadda MD and Timothy G Murray MD MBA

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

McCormick Place
Chicago, Illinois
Friday – Saturday, September 30 – October 1, 2022

Presented by:
The American Academy of Ophthalmology

Supported by an unrestricted educational grant from Genentech, Inc.

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On behalf of the American Academy of Ophthalmology and the American Society of Retina Specialists, the Macula Society, the Retina Society, and Club Jules Gonin, it is our pleasure to welcome you to Chicago and **Retina 2022: Retina Reimagined.**

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Disclosure list contains individual's relevant disclosures with ineligible companies. All relevant financial relationships have been mitigated.

Retina 2022 Contents

Retina Subspecialty Day Planning Group ii

CME vii

The Charles L Schepens MD Lecture ix

Faculty Listing x

How to Use the Audience Interaction Application xxiv

Program Schedule xxv

Section I: Vitreoretinal Surgery, Part I 1

Section II: Public Health, Education, and the Business of Retina 13

In These Unprecedented Times . . . 23

The Charles L Schepens MD Lecture:
Rediscovering AMD With Swept Source OCT Imaging 25

Section III: My Best Medical Retina Case 26

Section IV: Medical Retina and Chorioretinal Vascular Disease 27

Section V: Oncology 42

Section VI: The 2022 Debates 49

Section VII: Late Breaking Developments, Part I 55

Section VIII: First-time Results of Clinical Trials 56

Section IX: Imaging 66

Section X: Late Breaking Developments, Part II 77

Section XI: Neovascular AMD 78

Section XII: Uveitis 86

Section XIII: Diabetic Retinopathy 89

Section XIV: Pediatric Retina 105

Section XV: Gene- and Cell-Based Therapies 110

Section XVI: Artificial Intelligence 121

Section XVII: Nonexudative AMD 131

Section XVIII: Vitreoretinal Surgery, Part II 141

Section XIX: Surgical Videos—Cool Cases and Complications 147

Faculty Financial Disclosure 149

Presenter Index 161

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.

Retina Subspecialty Day Meeting 2022 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 and artificial intelligence strategies that are most helpful in the diagnosis and management of retinal conditions and discuss emerging developments in retinal imaging and diagnostics
- 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

Retina Subspecialty Day Meeting 2022 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.

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Subspecialty Day 2022 CME Credit

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

Friday Subspecialty Day Activity: Glaucoma, Pediatric Ophthalmology, Refractive Surgery, Uveitis, 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.

Attendance Verification for CME Reporting

Before processing your requests for CME credit, the Academy must verify your attendance at AAO 2022 and/or Subspecialty Day. Badges are no longer mailed before the meeting. Picking up your badge onsite will verify your attendance.

How to Claim CME

Attendees can claim credits online. For AAO 2022, you can claim CME credit multiple times, up to the 50-credit maximum, through Aug. 1, 2023. You can claim some in 2022 and some in 2023, or all in the same year. For 2022 Subspecialty Day, you can claim CME credit multiple times, up to the 12-credit maximum per day, through Aug. 1, 2023. You can claim some in 2022 and some in 2023, 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 2022 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 2022.

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

Rediscovering AMD With Swept Source OCT Imaging

Philip J Rosenfeld MD PhD

FRIDAY, SEPT. 30, 2022
9:47 AM – 10:07 AM

Philip J Rosenfeld MD PhD

Dr. Rosenfeld is Professor of Ophthalmology at the Bascom Palmer Eye Institute of the University of Miami Miller School of Medicine and a trained vitreoretinal specialist with a primary clinical and research interest in AMD. His major contributions include the clinical development of anti-VEGF therapies, the use of OCT-guided treatment using anti-VEGF therapy, the clinical development of OCT instruments, and the development of novel OCT algorithms for the diagnosis and management of macular diseases and for use as clinical trial endpoints. Dr. Rosenfeld has been the principal investigator and study chairman for numerous AMD clinical trials. Of note, he was a lead investigator in the Phase 1/2/3 ranibizumab trials and performed the 2-year PrONTO Study, in which he pioneered the use of OCT-guided, as-needed treatment as an alternative to monthly dosing with ranibizumab. He also pioneered the use of bevacizumab (Avastin) for exudative macular diseases with both systemic and intravitreal delivery. Since 2008, the Medicare cost savings alone from the use of bevacizumab and OCT-guided therapy for the treatment of neovascular AMD and other exudative eye diseases have far exceeded $50 billion in the United States alone, and far more worldwide.

Dr. Rosenfeld has over 300 peer-reviewed publications and a Scopus h-index of 73 (Google Scholar h-index of 86).

Dr. Rosenfeld has been involved in the clinical development of both spectral domain and swept source OCT (SS-OCT) instruments, along with their imaging algorithms. His OCT research team, in collaboration with Dr. Ruikang Wang's research group at the University of Washington in Seattle, have successfully used SS-OCT imaging and novel algorithms to image the different stages of AMD and develop prediction models for disease progression. The OCT anatomic features that have been studied include the identification and quantitation of drusen, including calcified drusen and reticular pseudodrusen (subretinal drusenoid deposits), and the use of optical attenuation coefficient OCT imaging to detect and measure macular hyperpigmentation, outer retinal thickness, basal laminar deposits, the formation and growth of geographic atrophy, choroidal thickness, and the choroidal vascularity index. Algorithms using SS-OCT angiography (SS OCT-A) have been developed to visualize and measure choriocapillaris perfusion, choriocapillaris thickness, Bruch membrane thickness, treatment-naive nonexudative macular neovascularization (MNV), and all the different types of exudative MNV. These algorithms have been used to develop OCT clinical trial anatomic endpoints for use in investigating novel therapies. With the ability to apply all these different algorithms to a single SS OCT-A scan, clinicians are now able to perform multimodal imaging of AMD using a single imaging modality.

Dr. Rosenfeld is an active member of numerous ophthalmologic societies and has received numerous awards. Of note, he was the recipient of the 75th Edward Jackson Award and Lecture from the American Academy of Ophthalmology (the Academy), the Russell Johnson Award for AMD Research from the University of Washington in Seattle, the Macula Society's Richard and Hinda Rosenthal Foundation Award, the Founders Award from the American Society of Retinal Specialists, the J Donald Gass Award from the Retina Society, the Heed Award, the Muse Award from Eye and Ear Foundation of the University of Pittsburgh, the Golden Medal Moacyr Álvaro from the Federal University São Paulo, the Nataraja Pillai Oration Award from the Vitreo-Retinal Society – India, the M H Rizvi Memorial Award from the Ophthalmological Society of Pakistan, the Lawrence A Yannuzzi Award from the International Retinal Imaging Society, and the Academy's Senior Achievement and Secretariat Awards. Since 2014, Dr. Rosenfeld has been named annually to the Ophthalmologist's Power List of the 100 most influential people in ophthalmology today, and in 2019, he was named to the Ophthalmologist's Power List of Inventors, which identified the 50 most influential people in ophthalmology.

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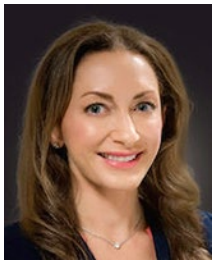

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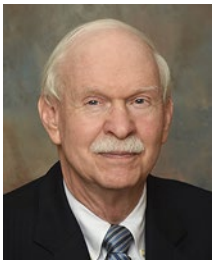

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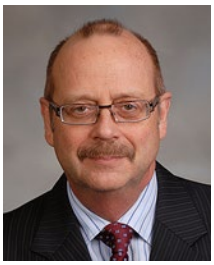

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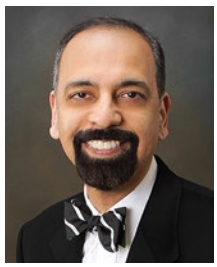

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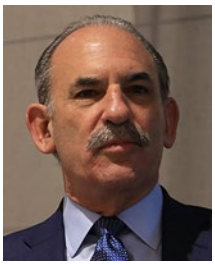

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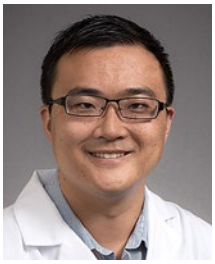

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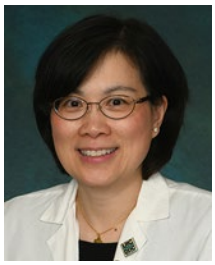

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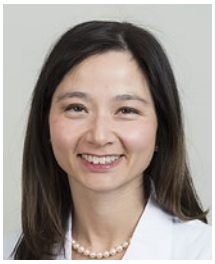

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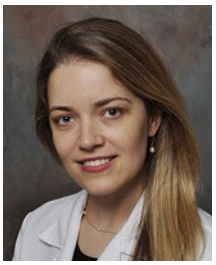

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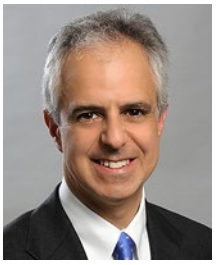

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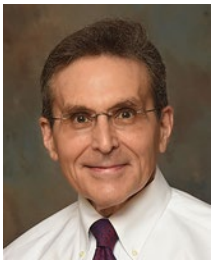

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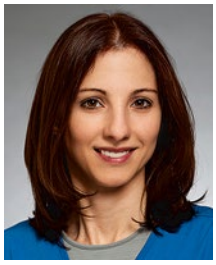

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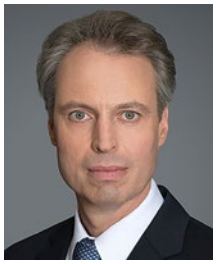

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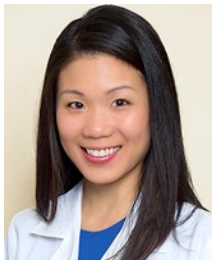

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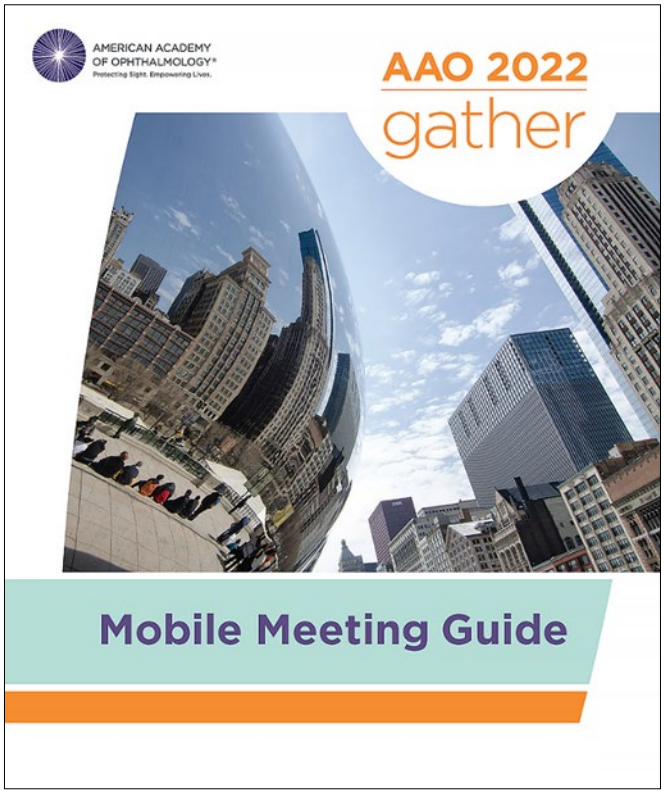

Retina 2022

Retina Reimagined

FRIDAY, SEPT. 30

8:00 AM	Welcome and Introductions	Srinivas R Sadda MD Timothy G Murray MD MBA	

Section I: Vitreoretinal Surgery, Part I

Moderator: Maria H Berrocal MD

Virtual Moderator Morning Sessions: Melissa D Neuwelt MD

8:04 AM	Is It Necessary to Peel Internal Limiting Membrane in Diabetic Vitrectomy?	Stanley Chang MD	1
8:10 AM	Early Vitrectomy for Complications of Proliferative Diabetic Retinopathy	Maria H Berrocal MD	2
8:16 AM	Simplifying Scleral-Fixated IOL Surgery	Christina Y Weng MD MBA	4
8:22 AM	Avoiding Critical Complications in Vitreoretinal Surgery	Steven T Charles MD	6
8:28 AM	Management of Asymptomatic Retinal Detachment	Harry W Flynn Jr MD	8
8:34 AM	Update on the Management of Rhegmatogenous Retinal Detachment	Rajeev H Muni MD	10
8:40 AM	Floater Rectomy: The Good, the Bad, and the Ugly	Jayanth S Sridhar MD	11
8:46 AM	Vitreoretinal Surgery Panel Panel Moderator: Gaurav K Shah MD Panelists: Philip J Ferrone MD, Marta Figueroa MD, Raymond Iezzi MD, and Lejla Vajzovic MD		12

Section II: Public Health, Education, and the Business of Retina

Moderator: Paul Sternberg Jr MD

9:01 AM	When Should a Retina Specialist Offer a Minimally Proven Investigational Treatment?	Paul Sternberg Jr MD	13
9:07 AM	The Future of In-Office Retinal Surgery	Tarek S Hassan MD	14
9:13 AM	Medical Moneyball? The Benefits and Pitfalls of Private Equity Retina Practice Consolidation	John T Thompson MD	18
9:19 AM	Health Policy Implications of Biosimilars	George A Williams MD	20
9:25 AM	Unconscious Gender Bias—What Is It, Where Are We At?	Tanya Trinh MBBS	22
9:31 AM	In These Unprecedented Times . . .	Sohail J Hasan MD PhD	23

The Charles L Schepens MD Lecture

9:36 AM	Introduction of the 2022 Charles L Schepens MD Lecturer	Stephen D McLeod MD	
9:41 AM	Rediscovering AMD With Swept Source OCT Imaging	Philip J Rosenfeld MD PhD	25
10:01AM	REFRESHMENT BREAK		

Section III:	**My Best Medical Retina Case**		
	Moderator: William F Mieler MD		
10:46 AM	Case Presentation	Anita Agarwal MD	26
10:49 AM	Discussion		
10:52 AM	Case Presentation	William F Mieler MD	26
10:55 AM	Discussion		
10:58 AM	Case Presentation	Amani Fawzi MD	26
11:01 AM	Discussion		
11:04 AM	Case Presentation	Jose S Pulido MD MS	26
11:07 AM	Discussion		
11:10 AM	Case Presentation	Lihteh Wu MD	26
11:13 AM	Discussion		
Section IV:	**Medical Retina and Chorioretinal Vascular Disease**		
	Moderator: Jacque L Duncan MD		
11:16 AM	What's New in Retinal Degenerations?	Jacque L Duncan MD	27
11:22 AM	Mimickers of AMD Every Ophthalmologist Should Know	Elliott H Sohn MD	29
11:28 AM	Noncancerous Masquerades	Phoebe Lin MD PhD	31
11:34 AM	Ultrawide-Field Angiography in Retinal Vein Occlusion: SCORE2 Experience	Barbara Ann Blodi MD	32
11:40 AM	Sickle Cell Retinopathy: Past Lessons, Future Directions	Adrienne Williams Scott MD	34
11:46 AM	Intervortex Vein Anastomoses in High Myopia and Their Implications for Other Chorioretinal Diseases	Kyoko Ohno-Matsui MD	35
11:52 AM	Choroidal Disturbance in Polypoidal Choroidal Vasculopathy: Insights From Dynamic Indocyanine Green Angiography	Gemmy Chui Ming Cheung MB BChir FRCOphth	38
11:58 PM	N-of-1 Clinical Trials: A Scientific Approach to Personalized Medicine for Patients With Rare Retinal Diseases Such as Retinitis Pigmentosa	Marco A Zarbin MD PhD FACS	39
12:04 PM	LUNCH		
Section V:	**Oncology**		
	Moderator: Evangelos S Gragoudas MD		
	Virtual Moderator Afternoon Sessions: Pradeep S Prasad MD		
1:36 PM	Current Status of "Liquid Biopsy" for Uveal Melanoma	Ivana K Kim MD	42
1:42 PM	Conditional Survival in Uveal Melanoma: This Is What the Patient Wants to Know	Carol L Shields MD	43
1:48 PM	Contemporary Precision Diagnosis and Management of Vitreoretinal Lymphoma	J William Harbour MD	45
1:54 PM	Retinal Toxicity of Novel Cancer Treatments	Jasmine H Francis MD	46
2:00 PM	Oncology Panel Discussion		48
	Panel Moderator: Prithvi Mruthyunjaya MD		
	Panelists: Michael M Altaweel MD, Jesse L Berry MD, Hakan Demirci MD, and Amy C Schefler MD		

Section VI: The 2022 Debates

Moderator: Jonathan L Prenner MD

2:15 PM	Home OCT Is Going to Be a Boon for Retinal Specialists	Anat Loewenstein MD	49
2:18 PM	Home OCT Is Going to Be the Bane of Retina Specialists	Carl C Awh MD	51
2:21 PM	Audience Vote		
2:22 PM	Monthly Intravitreal Therapy Is a Feasible Approach for Patients With Geographic Atrophy	Robert B Bhisitkul MD	52
2:25 PM	Monthly Intravitreal Therapy Is Impractical for Patients With Geographic Atrophy	Daniel F Martin MD	52
2:28 PM	Audience Vote		
2:29 PM	The Port Delivery System Will Be My Preferred Treatment for Neovascular AMD Patients Requiring Frequent Therapy	Caroline R Baumal MD	53
2:32 PM	Longer-Acting VEGF Agents Will Be My Preferred Treatment for Neovascular AMD Patients Requiring Frequent Therapy	Dante Pieramici MD	53
2:35 PM	Audience Vote		
2:36 PM	Surgical Peeling of Epiretinal Membrane Is Appropriate for Patients With Vision 20/25 or Better	Richard S Kaiser MD	54
2:39 PM	Surgical Peeling of Epiretinal Membrane Should Be Reserved for Patients With Vision Worse Than 20/40	Judy E Kim MD	54
2:42 PM	Audience Vote		
2:43 PM	REFRESHMENT BREAK		

Section VII: Late Breaking Developments, Part I

Moderator: Mark S Humayun MD PhD

Panelists: Robert L Avery MD, Suber S Huang MD MBA, Mathew W MacCumber MD PhD, and Shlomit Schaal MD PhD

3:24 PM	Intravitreal Aflibercept Injection 8 mg for Diabetic Macular Edema: 48-Week Results From the Phase 2/3 PHOTON Trial	David M Brown MD	55
3:29 PM	Interim Safety and Efficacy Data From a Phase 1 Clinical Trial of Sustained-release Axitinib Hydrogel Implant (OTX-TKI) in Wet AMD Subjects	Dilsher S Dhoot MD	55
3:34 PM	Discussion		
3:39 PM	ADVM-022 Intravitreal Gene Therapy for Neovascular AMD: OPTIC Phase 1 Study Update	Dante Pieramici MD	55
3:44 PM	Ranibizumab Biosimilar Candidate Compared to Reference Ranibizumab in Neovascular Age-Related Macular Degeneration	Anat Loewenstein MD	55
3:49 PM	Discussion		
3:54 PM	TALON, a Phase IIIb Study of Brolucizumab vs Aflibercept in a Matched (Treat & Extend) Regimen in nAMD	Peter J Kertes MD	55
3:59 PM	Real World Efficacy, Durability and Safety of Faricimab in Neovascular Age-Related Macular Degeneration: TRUCKEE Study	Ramanath Bhandari MD	55
4:04 PM	Intravitreal Aflibercept Injection 8 mg for Neovascular Age-related Macular Degeneration: 48-Week Results From the Phase 3 PULSAR Trial	Paolo Lanzetta MD	55
4:09 PM	Discussion		

Section VIII: First-time Results of Clinical Trials

Moderator: Diana V Do MD

Panelists: Eleonora G Lad MD PhD, Colin A McCannel MD, and Demetrios Vavvas MD

4:09 PM	GATHER2 Phase 3 Efficacy Results	Arshad M Khanani MD	56
4:15 PM	GATHER2 Phase 3 Safety Results	Jeffrey S Heier MD	58
4:21 PM	Treatment of Geographic Atrophy Secondary to AMD With Pegcetacoplan: Two-Year Outcomes From the Randomized Phase 3 DERBY and OAKS Trials	Charles C Wykoff MD PhD	59
4:27 PM	SCORE2 5-Year Visual Acuity Results	Ingrid U Scott MD MPH	61
4:33 PM	DRCR Retina Network: Protocol AC Results	Chirag D Jhaveri MD	63
4:39 PM	KSI-301 Anti-VEGF Antibody Biopolymer Conjugate for Retinal Vein Occlusion: Primary and Secondary 24-Week Efficacy and Safety Outcomes of the BEACON Phase 3 Pivotal Study	Michael A Singer MD	65
4:45 PM	Discussion		
4:55 PM	Closing Remarks	Srinivas R Sadda MD Timothy G Murray MD MBA	
4:56 PM	ADJOURN		

SATURDAY, OCT. 1

8:00 AM	Opening Remarks	Srinivas R Sadda MD Timothy G Murray MD MBA	

Section IX: Imaging

Moderator: Richard B Rosen MD

Virtual Moderator Morning Sessions: Ghazala A Datoo O'Keefe MD

8:04 AM	Update on OCT Angiography	Nadia Khalida Waheed MD	66
8:10 AM	Can We Use OCT Angiography Instead of Fluorescein Angiography for Nonproliferative Diabetic Retinopathy Evaluation and PDR Detection?	Ramin Tadayoni MD PhD	67
8:16 AM	Home OCT	Nancy M Holekamp MD	69
8:22 AM	Update on Intraoperative OCT	Lejla Vajzovic MD	71
8:28 AM	Imaging the Vitreous	Richard F Spaide MD	74
8:34 AM	Mitochondrial Imaging Insights Into Retinal Diseases	Rishi P Singh MD	75
8:40 AM	Imaging Panel Discussion Panel Moderator: Jay S Duker MD Panelists: Marion Ronit Munk MD PhD, Giuseppe Querques MD, Nadia Khalida Waheed MD, and Sandrine Zweifel MD		76

Section X: Late Breaking Developments, Part II

Moderator: Sharon D Solomon MD

Panelists: Rajendra S Apte MD PhD, Catherine A Cukras MD PhD, Sunir J Garg MD FACS, and Hendrik P Scholl MD

8:55 AM	Phase 1 Study of JNJ-81201887 Gene Therapy in Geographic Atrophy (GA) Due to Age-related Macular Degeneration (AMD)	Michael Nathan Cohen MD	77
9:00 AM	Ph1/2 AAV5-RPGR (Botaretigene Sparoparvovec) Gene Therapy Trial in RPGR-associated X-linked Retinitis Pigmentosa (XLRP)	Michel Michaelides MD	77

9:05 AM	Discussion		
9:10 AM	Ellipsoid Zone Preservation in Patients with Age-Related Macular Degeneration Treated with Subcutaneous Elamipretide	Sunil K Srivastava MD	77
9:15 AM	Safety and Efficacy of SAR439483 in Patients with Leber Congenital Amaurosis Caused by Biallelic Mutations in GUCY2D (LCA1)	Christine Nichols Kay MD	77
9:20 AM	A 2-year Phase 1b/2 Study of the Safety and Tolerability of Tinlarebant in Adolescent STGD1 Subjects: Interim Findings	John Grigg MBBS	77
9:25 AM	Discussion		

Section XI: Neovascular AMD

Moderator: TBA

9:30 AM	Management of Non-neovascular Fluid in AMD: Observe and Extend	David Sarraf MD	78
9:36 AM	Port Delivery System Long-term Portal Extension Data: Three-Year Follow-up From the Phase 3 Archway Study	Carl D Regillo MD FACS	79
9:42 AM	Biosimilar Trials for Retinal Diseases: Recent Clinically Relevant Safety and Efficacy Results	Susan B Bressler MD	81
9:48 AM	Development of a Disease Activity Scale for Neovascular AMD	Usha Chakravarthy MBBS PhD	82
9:54 AM	Long-term Effect of the Anti-VEGF Treatment: A 12-Year Experience	Giovanni Staurenghi MD	83
10:00 AM	Retinal Microvascular Abnormalities Masquerading as Neovascular AMD	K Bailey Freund MD	84
10:06 AM	Neovascular AMD Panel Discussion Panel Moderator: Andrew A Moshfeghi MD MBA Panelists: Jay K Chhablani MBBS, Christina J Flaxel MD, James C Folk MD, Timothy W Olsen MD, and Dimitra Skondra MD		85
10:21 AM	REFRESHMENT BREAK and AAO 2022 EXHIBITS		

Section XII: Uveitis

Moderator: Quan Dong Nguyen MD

10:56 AM	Uveitic Macular Edema	Douglas A Jabs MD MBA	86
11:02 AM	Management of Acute Retinal Necrosis in 2022	Thomas A Albini MD	87
11:08 AM	Uveitis Panel Discussion Panel Moderator: Sunil K Srivastava MD Panelists: Nisha Acharya MD, Debra A Goldstein MD, Lucia Sobrin MD, and Edmund Tsui MD		88

Section XIII: Diabetic Retinopathy

Moderator: Lloyd M Aiello MD PhD

11:23 AM	Is the Retinal Far Periphery Important for Diabetic Retinopathy? Lessons From DRCR Retina Network Protocol AA	Jennifer K Sun MD	89
11:29 AM	Analysis of Anatomic Changes in the Kingfisher Trial: Brolucizumab vs. Aflibercept Treatment in Eyes With Diabetic Macular Edema	Michael S Ip MD	91
11:35 AM	Anti-VEGF/anti-Ang2 Year 2 Outcomes for Diabetic Macular Edema and Neovascular AMD	Jennifer Irene Lim MD	94
11:41 AM	Anti-VEGF Prevention for Severe Nonproliferative Diabetic Retinopathy: A Tale of Two Perspectives	Neil M Bressler M	96
11:47 AM	Real-World Data: What if Diabetic Retinopathy Patients Are Lost to Follow-up?	J Fernando Arevalo MD PhD FACS	97

11:53 AM	The Role of Inflammation in Diabetic Macular Edema	Baruch D Kuppermann MD PhD	99
11:59 AM	Drugs in the Pipeline for Diabetic Eye Disease	David S Boyer MD	101
12:05 PM	Diabetes Panel Discussion Panel Moderator: Jennifer K Sun MD Panelists: Alain Gaudric MD, Dennis M Marcus MD, Purnima S Patel MD, Aleksandra V Rachitskaya MD, and John A Wells III MD		103
12:20 PM	LUNCH and AAO 2022 EXHIBITS		

Section XIV: Pediatric Retina

Moderator: Antonio Capone Jr MD

Virtual Moderator Afternoon Sessions: Brittni Ashton Scruggs MD

1:40 PM	What's New in the ICROP3 Classification of ROP?	Mary Elizabeth Hartnett MD FACS	105
1:46 PM	Management of Persistent Avascular Retina and Reactivation in Retinopathy of Prematurity	R V Paul Chan MD	107
1:52 PM	Three Decades of ROP in an Inner City Hospital	Audina M Berrocal MD	108
1:58 PM	Pediatric Retina Panel Discussion Panel Moderator: Yoshihiro Yonekawa MD Panelists: Kimberly A Dresner MD, G Baker Hubbard MD, Darius M Moshfeghi MD, Aaron Nagiel MD PhD, and Irena Tsui MD		109

Section XV: Gene- and Cell-Based Therapies

Moderator: David N Zacks MD PhD

2:19 PM	Gene Therapy for Atrophic AMD 2022	Allen C Ho MD	110
2:25 PM	Gene Therapy for Neovascular AMD	Peter A Campochiaro MD	114
2:31 PM	Ocular Inflammation in Retinal Gene Therapies	Glenn C Yiu MD PhD	116
2:37 PM	Stem Cell Therapy for Retinal Disease: Where Are We Now?	Susanna S Park MD PhD	117
2:43 PM	Optimizing Submacular Injections: Cell, Viral, and Recombinant Therapeutics	Steven D Schwartz MD	119

Section XVI: Artificial Intelligence

Moderator: Tien Yin Wong MBBS

2:49 PM	Solving the Last Mile Problem: Training Deep Learning Models to Work With New Retinal Imaging Devices Without Human Annotations	Aaron Y Lee MD	121
2:55 PM	Application of AI in Predicting Cardiovascular and Neurological Diseases From Eye Images	Tien Yin Wong MBBS	122
3:01 PM	Defining the Fluid Problem in Neovascular AMD: To Dry, or Not to Dry?	Justis P Ehlers MD	124
3:07 PM	Deep Learning for Biomarkers in Non-neovascular AMD	Srinivas R Sadda MD	125
3:13 PM	The Role of AI-Guided OCT Imaging in Geographic Atrophy	Ursula M Schmidt-Erfurth MD	128
3:19 PM	What the Retina Specialist Should Know About Activities at the National Eye Institute in 2022	Michael F Chiang MD	130
3:25 PM	REFRESHMENT BREAK and AAO 2022 EXHIBITS		

Section XVII: Nonexudative AMD

Moderator: Johanna M Seddon MD

4:05 PM	Why Does Drusen Regression Herald Geographic Atrophy?	Mark W Johnson MD	131
4:11 PM	Macular Atrophy With Long-term Continuous vs. Bolus Anti-VEGF Therapy in Eyes With Neovascular AMD	Glenn J Jaffe MD	133
4:17 PM	The Role of Novel Functional Assessments in AMD: Only for Clinical Research, or the Future of Clinical Care?	Karl G Csaky MD	135
4:23 PM	New Treatments for Dry AMD	Peter K Kaiser MD	138
4:29 PM	Developing Systemic Biomarkers for AMD	Joan W Miller MD	139

Section XVIII: Vitreoretinal Surgery, Part II

Moderator: Jean-Pierre Hubschman MD

4:35 PM	Surgical Management of Retinal Detachment After Open Globe Injury	Dean Eliott MD	141
4:41 PM	Small Uveal Melanoma: The Role of the Vitreoretinal Surgeon	Timothy G Murray MD MBA	143
4:47 PM	The Role of Vitreoretinal Surgical Techniques in Management of Uveal Melanoma	Tara A McCannel MD	144
4:53 PM	Current Concepts in Macular Hole Surgery	Sophie J Bakri MD	145
4:59 PM	Advances in Technology and Imaging in Vitreoretinal Surgery	David R Chow MD	146

Section XIX: Surgical Videos—Cool Cases and Complications

Moderator: Kourous Rezaei MD

5:05 PM	Failed Large Macular Hole	Tongalp H Tezel MD	147
5:06 PM	Discussion		
5:09 PM	Retinal Detachment in Osteodentokerathoprosthesis	Carl C Claes MD	147
5:10 PM	Discussion		
5:13 PM	Hydatid Cyst	Sengul C Ozdek MD	147
5:14 PM	Discussion		
5:17 PM	Subretinal Silicone Oil	Ehab N El Rayes MD PhD	147
5:18 PM	Discussion		
5:21 PM	Intraocular Foreign Body	Stanislao Rizzo MD	147
5:22 PM	Discussion		
5:25 PM	Closing Remarks	Srinivas R Sadda MD Timothy G Murray MD MBA	
5:26 PM	ADJOURN		

Is It Necessary to Peel Internal Limiting Membrane in Diabetic Vitrectomy?

Stanley Chang MD

Introduction

Whether internal limiting membrane (ILM) should be stained and peeled routinely during vitrectomy for diabetic retinopathy remains a matter of controversy. Advocates for peeling ILM argue that the incidence of macular edema and epiretinal formation is less. Nonpeelers argue that Müller cells that are injured after ILM peeling play a vital role in maintaining retinal homeostasis, and that retinal ganglion cells may be lost over time. The purpose of this investigation was to study the effects of ILM peeling during diabetic vitrectomy and to review the evidence available supporting the benefits of ILM peeling.

Results

The surgical peeling of the ILM removes the foot plates of Müller cells and pieces of retinal nerve fiber layer at the surface of the retina. Müller cells traverse the entire thickness of the retina and play a vital role in retinal metabolism. In the normal retina, these cells recycle neurotransmitters, prevent glutamate toxicity, participate in retinoid recycling, regulate nutrient stores such as glycogen and ATP, and maintain the blood–retinal barrier. In eyes with continued hyperglycemia, there is an increase in glial fibrillary activating protein (GFAP), resulting in gliosis. Stressed Müller cells release chemokines and cytokines, such as vascular endothelial growth factor, interleukins, and caspase activators, resulting in capillary damage.[1] One additional consideration is that the retinal thickness in patients with long-standing diabetes is often less on OCT scan (neurovascular effect?), and patients undergoing vitrectomy are often younger than patients with epiretinal membranes.

The clinical outcomes after diabetic vitrectomy for complications of proliferative diabetic retinopathy (PDR) were reported in a series of 207 eyes. In eyes that underwent ILM peeling (n = 105), the average VA was better than in the group that did not have ILM peeling (n = 102) (P < .01).[2] Furthermore, there was less macular edema and epiretinal membrane formation in the ILM-peeling group. The follow-up period was 6 months. In studies reporting the value of ILM peeling for diabetic macular edema (DME), a small series on nonrandomized patients who had treatment-naïve DME showed a marked improvement, from preop average central foveal thickness of 595 microns to an average of 266 microns postoperatively.[3] However, other randomized clinical trials and meta-analysis of ILM peeling for diabetic macular edema have not shown a clear benefit to ILM peeling for diabetic macular edema. In one series, a proportion of ILM-peeled patients suffered visual loss. The inclusion criteria and follow-up periods for these trials vary.

Cases will be presented that demonstrate the outcomes of diabetic vitrectomy with and without ILM peeling.

References

1. Coughlin BA, Feenstra DJ, Mohr S. Müller cells and diabetic retinopathy. *Vision Res*. 2017; 139:93.
2. Rush RB, Del Valle Penella A, Reinauer RM, et al. Internal limiting membrane peeling during vitrectomy for diabetic vitreous hemorrhage. *Retina* 2021; 41:1118.
3. Michelewska Z, Stewart MB, Landers MB, et al. Vitrectomy in the management of diabetic macular edema in treatment-naïve patients. *Can J Ophthalmol*. 2018; 53:402.
4. Nakajima T, Roggia MF, Noda Y, Ueta T. Effect of internal limiting membrane peeling during vitrectomy for diabetic retinopathy: a systematic review and meta-analysis. *Retina* 2015; 35:1719.
5. Kumagai K, Hangai M, Ogino N, Larson E. Effect of internal limiting membrane peeling on long-term visual outcomes for diabetic macular edema. *Retina* 2015; 35:1422.
6. Hartley KL, Smiddy WH, Flynn Jr HW, Murray TG. Pars plana vitrectomy with internal limiting peeling for diabetic macular edema. *Retina* 2008; 28:410.

Early Vitrectomy for Complications of Proliferative Diabetic Retinopathy

María H Berrocal MD

I. The Diabetes Epidemic in the United States

A. Over 34 million diabetics in 2018, 7.3 million undiagnosed

B. Type 2 diabetes among persons 44 years of age or younger is expected to increase 50%.

C. Over 6,000 new cases of type 2 diabetes in children and adolescents

II. Diabetes is the most expensive chronic condition in the U.S. (CDC).

A. 25% of all health-care costs are spent on diabetes.

B. $237 billion in direct medical costs plus $90 billion on reduced productivity

C. 48%-64% of lifetime medical costs for a person with diabetes are for diabetic complications.

III. The cost utility of pars plana vitrectomy (PPV) for proliferative diabetic retinopathy (PDR) at 2 years is similar to that of panretinal photocoagulation (PRP) but significantly lower than that of intravitreal ranibizumab in the United States.[1]

A. Five-year Protocol S: Half of eyes treated with PRP require supplemental treatment, 19% require vitrectomy.

B. Eyes treated with PPV remain stable for years, with minimal progression of retinopathy.

C. Removal of the hyaloid eliminates progression to tractional retinal detachment (TRD).

D. Cost of vitrectomy outside of the U.S. fluctuates between $1500 and $5000, making it a very cost-effective treatment modality.

IV. In the Diabetic Retinopathy Vitrectomy Study, eyes with vitreous hemorrhage were randomized to early or late vitrectomy if nonclearing (1985).

A. Eyes in patients with type 1 diabetes showed better outcomes with early vitrectomy. Type 1 diabetics are younger and have an attached hyaloid.

B. Eyes with early vitrectomy are more likely to have a final VA of 20/40 or better at 2 years.

C 20% of eyes ended with NLP VA.

V. The attached vitreous is the enemy.

A. Progression of diabetic retinopathy is dependent on the status of the vitreous.

B. Retinopathy progression at 3 years: 403 patients[2]

1. No posterior vitreous detachment (PVD): 44% had progression of retinopathy.

2. PVD with collapse: 0% showed progression.

3. Partial PVD with thickened posterior hyaloid: 100% showed progression.

C. Eyes with total PVD stabilize long term, do not develop TRD or disease progression.

VI. PRP is not a permanent solution in diabetics with attached hyaloid.

Protocol S at 5 years: mean age, 51 years

A. 46% developed vitreous hemorrhage.

B. 12% developed TRD.

C. 19% required PPV.

D. 4% developed neovascular glaucoma.

VII. Anti-VEGF should be used with caution as sole treatment in diabetics with attached hyaloid-TRD.

Protocol AB: 205 eyes with vitreous hemorrhage randomized to aflibercept vs. vitrectomy with PRP, men age 57 years

A. 17% of eyes had type 1 diabetes; 42% and 55% of eyes had previous PRP.

B. Twice as many eyes in the aflibercept arm developed TRD.

C. 49% of eyes in the aflibercept arm developed recurrent vitreous hemorrhage vs. 15% in the vitrectomy arm.

D. 29% of eyes in the aflibercept arm had persistent neovascularization vs. 3% in the vitrectomy arm.

VIII. Missed appointments and loss to follow-up are common among diabetic patients.

A. Complete loss to follow-up at 6 months was 54%; and at 1 year, 52.4%.

B. Eyes treated with anti-VEGF did worse than PRP-treated eyes when lost to follow-up. 33% treated with anti-VEGF developed TRD vs. 2% of PRP-treated eyes lost to follow-up.

IX. Diabetic patients younger than 50 years whose worse eye is treated with vitrectomy at 8 years follow-up showed better visual acuity in the vitrectomized eye, and significantly less procedures required ($N = 60$).

A. Mean postop VA among the vitrectomized arm was 20/80 vs. 20/400 in the nonvitrectomized arm.

B. 8% of vitrectomized eyes ended with VA HM or less vs. 36% in the nonvitrectomized arm.

X. The Fellow-Eye Study showed 25%-40% of fellow eyes in patients undergoing a vitrectomy in one eye will need it in the other eye.

XI. Removal of the hyaloid is easier in eyes with non-severe PDR compared to eyes with areas of TRD.

Vitrectomy should not be seen as a last-resort treatment and may be considered in eyes with an attached hyaloid to prevent progression of disease and retinal detachment.

XII. Advantages of Early Vitrectomy in Diabetic Retinopathy

A. Prevents TRD and TRRD

B. Stabilizes eyes long term

C. Reduces complications and subsequent treatments

D. Treatment burden and risk of loss to follow-up are reduced.

E. Cost is significantly less than anti-VEGF treatments.

XIII. Conclusions

A. The status of the hyaloid is crucial when determining treatment modalities for eyes with complications of diabetes.

B. Vitrectomy with removal of the hyaloid can provide long-term stability to eyes with diabetic retinopathy.

References and Selected Readings

1. Lin J, Chang JS, Yannuzzi NA, Smiddy WE. Cost evaluation of early vitrectomy versus panretinal photocoagulation and intravitreal ranibizumab for proliferative diabetic retinopathy. *Ophthalmology* 2018; 126(9):1393-1400.
2. Ono R, Kakehashi A, Yamagami H, et al. Prospective assessment of proliferative diabetic retinopathy with observations of posterior vitreous detachment. *Int Ophthalmol*. 2005; 26:15-19.
3. 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; 136:1138-1148.
4. Vote BJ, Gamble GD, Polkinghorne PJ. Auckland Proliferative Diabetic Vitrectomy Fellow Eye Study. *Clin Exp Ophthalmol*. 2004; 32:397-403.
5. Maguire MG, Liu D, Bressler SB, et al. Lapses in care among patients assigned to ranibizumab for proliferative diabetic retinopathy: a post hoc analysis of a randomized clinical trial. *JAMA Ophthalmol*. 2021; 139:1266-1273.
6. Berrocal MH, Acaba-Berrocal L. Early pars plana vitrectomy for proliferative diabetic retinopathy: update and review of current literature. *Curr Opin Ophthalmol*. 2021; 32:203-208.
7. Glassman AR, Beaulieu WT, Maguire MG, et al. Visual acuity, vitreous hemorrhage, and other ocular outcomes after vitrectomy vs aflibercept for vitreous hemorrhage due to diabetic retinopathy: a secondary analysis of a randomized clinical trial. *JAMA Ophthalmol*. 2021; 139:725-733.

Simplifying Scleral-Fixated IOL Surgery

Christina Y Weng MD MBA

I. Background

A. Secondary IOL options in absence of capsular support include anterior chamber, iris-sutured, iris-fixated, scleral-sutured, and sutureless scleral-fixated.

B. The sutureless scleral-fixated IOL has gained popularity in recent years.[1-3]

1. Double-needle technique described by Japanese surgeon Dr. Shin Yamane[4] in 2017

2. Modifications of the Yamane technique have been described by vitreoretinal surgeons.[5]

II. Trocar-based sutureless scleral-fixated IOL surgery has advantages and disadvantages.

A. Advantages

1. Effective and efficient[6,7]

2. Can be completed by single surgeon and combined with vitrectomy

B. Disadvantages

1. Long-term stability data are limited.

2. Complications can occur. For example, reverse pupillary block occurred in 3% of patients without a peripheral iridotomy, and IOL dislocation affected 6.6% of patients in 1 large series.[7]

3. Can be technically challenging when first learning technique

III. Surgical Pearls for Trocar-Based Sutureless Scleral-Fixated IOL Surgery[8]

A. Preoperative

1. Ensure mobile, healthy conjunctiva.

2. Counsel patient regarding risk of residual refractive error, especially if rescuing IOL.

3. MA60AC (Alcon), ZA9003 (Johnson & Johnson), CT Lucia 602 (Carl Zeiss Meditec) can all be used, although not approved for sulcus placement. Aim for plano refractive target if externalizing 2.5 mm posterior to limbus.

4. Avoid creating bullous conjunctiva with retrobulbar anesthesia block.

B. Intraoperative

1. Haptics can be externalized through 25- or 27-gauge cannulae.

2. Mark exactly 180° apart using a corneal marker centered around the limbus, not the pupil, and then mark 2-2.5 mm posterior to the limbus.

3. Place externalizing cannulae at 1 and 7 o'clock in right eyes, 11 and 5 o'clock in left eyes. Ensure that entry angle and tunnel length are symmetrical to avoid tilt/decentration.

4. Place infusion line inferonasally in left eyes.

5. Perform a close peripheral shave in the meridians of externalization.

6. Ensure complete removal of capsular bag remnants to prevent tilt.

7. Use hand-to-hand technique (see Figure 1) to grasp anywhere along the leading haptic and then pass to externalizing forceps.

a. When externalizing, grasp tightly at the very tip of the haptic.

b. Ask assistant to stabilize already-externalized haptic with non-toothed forceps when externalizing the other haptic.

8. If satisfied with centration, elevate haptic tip off ocular surface and hold low-temp cautery near tip to burn bulb, then tuck bulbs so they sit just inside the scleral tunnel. Minor adjustments are possible by trimming the haptics to address *mild* decentration.

9. Constrict pupil and consider a peripheral iridotomy to prevent reverse pupillary block.

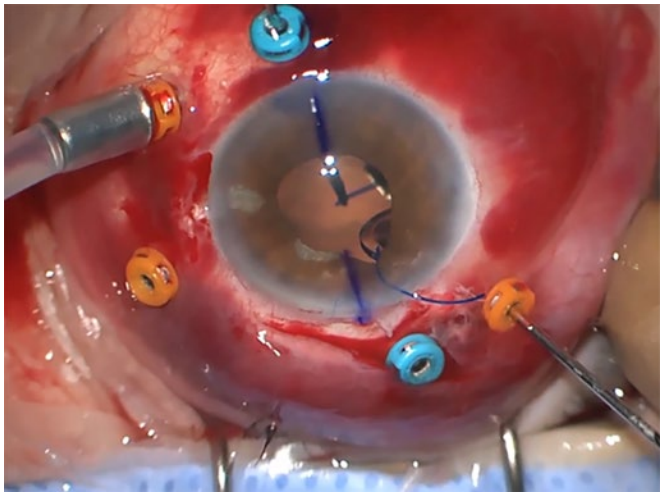

Figure 1. Hand-to-hand technique illustrated in a 23/25-gauge trocar-based sutureless scleral-fixated IOL surgery where 2 nonserrated retinal forceps are used to manipulate the haptic in a controlled manner so that the haptic tip can be grasped and ultimately externalized. Figure courtesy of Christina Y Weng MD MBA.

C. Postoperative

Consider avoiding dilation until postoperative Week 1 visit.

IV. Conclusion

A. Trocar-based sutureless scleral-fixated IOL surgery can be effective and quite efficient.

B. Data on long-term stability and optimal IOL calculation formula for this technique are needed, but large case series have reported excellent overall outcomes thus far.[7]

References

1. Nudleman E, Yonekawa Y, Prenner JL. Sutureless transscleral fixation of secondary intraocular lenses. *Curr Opin Ophthalmol.* 2018; 29(3):210-216.
2. Thanos A, Lau-Sickon LK, Wolfe JD, Hassan TS. Three port sutureless posterior chamber intraocular lens intrascleral fixation: a novel approach. *Retina* 2019; 39 suppl 1:16-20.
3. Prasad S. Transconjunctival sutureless haptic fixation of posterior chamber IOL: a minimally traumatic approach for IOL rescue or secondary implantation. *Retina* 2013; 33(3):657-660.
4. Yamane S, Sato S, Maruyama-Inoue M, Kadonosono K. Flanged intrascleral intraocular lens fixation with double-needle technique. *Ophthalmology* 2017; 124(8):1136-1142.
5. Walsh MK. Sutureless trocar-cannula-based transconjunctival flanged intrascleral intraocular lens fixation. *Retina* 2017; 37(11):2191-2194.
6. Stem MS, Wa CA, Todorich B, Woodward MA, Walsh MK, Wolfe JD. 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.
7. Patel KG, Yazdani A, Abbey AM. Twenty-five and twenty-seven-gauge sutureless intrascleral fixation of intraocular lenses: clinical outcomes and comparative effectiveness of haptic flanging in a large single-surgeon series of 488 eyes. *Retina* 2021; 41(12):2485-2490.
8. Weng CY. Simplifying sutureless scleral-fixated intraocular lens surgery. *Retinal Physician* 2021; 18(4):24-28.

Avoiding Critical Complications in Vitreoretinal Surgery

Steve Charles MD

I. Infusion Cannula Issues

II. General Considerations

A. If you cannot see the infusion cannula tip with the microscope (not the naked eye and endoilluminator), you cannot infuse with it; depress cannula with smooth forceps to view infusion cannula tip with microscope to check for overlying tissue.

B. Avoiding suprachoroidal and subretinal infusion.

C. If preoperative hypotony, choroidals, or suprachoroidal hemorrhage

1. Pre-firm eye with 30-gauge needle and BSS.

2. Place cannula perpendicular to scleral surface; not angulated scleral tunnel.

3. Use a 6-mm infusion cannula.

D. Construct a sufficient length, upright service loop when affixing infusion tubing to drape.

1. Avoid previous sclerotomy sites because cannula can be dislodged if excessive sclerotomy size.

III. Lens Capsule Management

A. If lensectomy is required; remove *all* of the capsule with textured end-grasping forceps.

B. Retained capsule causes

1. Epiciliary tissue leading to hypotony and phthisis

2. Concave iris, fixed pupil

3. Inflammation from neocortex

4. Anterior loop vitreoretinal traction

5. Fibrosis of inferior peripheral iridectomy in silicone oil cases

IV. Proliferative Vitreoretinopathy (PVR): Common Mistakes

A. Relaxing retinotomy (Machemer) leaves retina anterior to circumferential cut, which causes epiciliary tissue, hypotony, and increased anterior PVR; retinectomy (Charles) removes retina anterior to circumferential cut and produces better outcomes.

B. Retinectomy under perfluoro-n-octane (PFO) often causes subretinal/subfoveal PFO; retinectomy under air is better.

C. Retinectomy under BSS can result in unnecessary, inadequate, or excessive retinectomy.

D. Scleral buckle has no benefit in retinectomy cases.

E. Excessive, intense retinopexy causes PVR.

F. Removing oil to reoperate for recurrent PVR or epimacular membrane is not required; surgery under oil is more efficient and effective.

V. PVR Essentials

A. Use forceps membrane peeling with ILM forceps, *not* pics and spatulas.

B. Liquid perfluorocarbon is unnecessary and can result in subfoveal PFO.

C. Avoid scleral buckles; they cause:

1. Axial myopia (average 2.75 D; Michels et al)

2. Strabismus (50% increase in phorias and tropias; Michels et al)

3. Ocular surface disorder (poor conjunctival closure, removing corneal epithelium)

4. Adherence of conjunctiva, Tenon capsule, and episclera, which significantly impact subsequent glaucoma filtration procedures

5. Increased operating time and use of general anesthesia

6. Pain

VI. Reducing Postop PVR

A. Never use cryopexy.

B. Use low-intensity laser applications, not "burns."

C. Treat retinal breaks with confluent laser.

D. If inflammatory PVR, use silicone oil for rhegmatogenous confinement, which enables retinopexy avoidance.

VII. Diabetic Traction Retinal Detachment (TRD) Essentials

A. Do not forcefully construct a posterior vitreous detachment.

B. Learn to use delamination with curved scissors; do not attempt to manage tabletop TRD (broad zones of adherence) with cutter alone.

C. Do not attempt to peel highly adherent membranes; use delamination.

D. Use minimal if any diathermy; control bleeding by raising IOP.

E. Avoid iatrogenic retinal breaks and retinectomy if possible because they lead to silicone oil use.

1. Silicone oil has a low oxygen extraction ratio and increases retinal hypoxia.

2. Silicone oil causes silicone oil macular edema (SOME).
3. Silicone oil emulsification glaucoma is common.
4. Silicone oil sequesters vascular endothelial growth factor (VEGF), basic fibroblast growth factor, reactive Müller cells, cytokines, and fibronectin at retina–oil interface.
5. Silicone oil prevents anti-VEGF access to retina.

F. Do not use scleral buckles.

VIII. Giant Retinal Breaks

A. Common problem: retinal slippage during PFO–oil or PFO–gas exchange

1. Solution: medium-term PFO (2 weeks) for inferior, nasal, or temporal giant breaks. Patients can stand, sit, work, recline, and fly with inferior breaks.
2. Lie on side for temporal or nasal giant breaks.
3. Prone or face-down positioning prohibited.

B. Avoid:

1. Scleral buckles
2. Combined phaco unless cataract obscures visualization
3. Short needle to inject PFO causes multiple bubbles; use dual-bore cannula because it enables single bubble.
4. Excessive retinopexy causes PVR.
5. Cryo

IX. Superior Giant Retinal Tears

A. Keep 27-gauge extrusion cannula tip at oil or gas interface with PFO in periphery during exchange; must remove all BSS, subretinal fluid, and liquid vitreous before PFO to avoid slippage (must follow interface down during exchange).

B. Keep focus on cannula tip as exchange proceeds posteriorly to optimize view of interface (minimal difference in index of refraction between PFO and oil).

C. PFO–gas exchange *or* PFO–silicone oil exchange if PVR for superior giant retinal tear.

D. Direct PFO–oil exchange options

1. Viscous fluid control (VFC) @80 psi to inject oil through MedOne Oil infusion tubing over nonvalved infusion cannula and 27-gauge extrusion cannula without soft-tip in the other hand to remove PFO.
2. Chandelier illumination; VFC @80 psi through superotemporal cannula with short, thin-walled, low-resistance cannula and 27-gauge extrusion cannula without soft-tip in the other hand to remove PFO.

X. Avoiding Subfoveal PFO

A. Inject PFO slowly with MedOne dual-bore cannula, keeping tip of cannula in contact with highest point of PFO bubble as it expands upward; follow focus at high magnification to see interface.

B. Never use PFO if rigid retina and posterior breaks.

XI. Managing Air or Silicone Oil in Anterior Chamber of Phakic or IOL Eye

A. Fill anterior chamber with Viscoat through limbal sideport, starting with tip of cannula on opposite side of the eye, withdrawing cannula while injecting.

B. Allow air or silicone oil to egress through the sideport.

C. Do not remove Viscoat (Kirk Packo).

D. Use topical or oral carbonic anhydrase inhibitor to control IOP.

E. Do not substitute viscoelastics; use Viscoat or postop IOP can be excessive.

XII. Gas Mistakes

A. Do not inject 100% gas after full or partial fluid–air exchange.

B. Always use isoexpansive concentration of SF_6 (25%) via fluid–air exchange followed by air–gas exchange.

C. Never use SF_6 concentrations higher than 25%.

D. Do not use C_3F_8. There is no advantage for macular holes or retinal detachments. (C_3F_8 is mandatory for pneumatic retinopexy.)

E. Air duration insufficient for retinal detachments, full- or partial-thickness macular holes, or macular schisis

F. Do not use air or gas in epimacular membrane cases unless macular hole, macular schisis, or retinal break; air/gas does not reduce/eliminate folds.

G. Pulling up buckle after gas or especially silicone oil is injected can result in over-pressurization.

XIII. Air–Silicone Exchange

A. Do not remove one cannula, inject oil, and expect air to re-enter the infusion system; over-pressurization can occur.

B. Inject oil through superotemporal cannula using VFC with short, thin walled cannula; maintain 25-45 mmHg air infusion and allow air to egress through superonasal vented cannula; clamp infusion tubing when oil enters infusion tubing; keep vent at apex of decreasing air bubble to produce a normotensive full fill; stop when oil comes out vent; check tactile IOP.

Management of Asymptomatic Retinal Detachment

Outcomes of Initial Nonsurgical Management

Harry W Flynn Jr MD and Jesse D Sengillo MD

I. Asymptomatic Retinal Detachments (ARDs)
   A. Definition: Rhegmatogenous retinal detachments identified in patients who lack symptoms of flashes or visual field changes and who have unaffected central VA
   B. Observational management for ARDs is not discussed in the American Academy of Ophthalmology Preferred Practice Patterns.

II. Previously Reported Outcomes of Patients With Initial Observational Management of ARDs
   A. Review of the literature (see Table 1)
   B. Published studies: Jarrett (1988)[2], Brod et al (1995)[3], Byer (2001)[4]

III. Studies at Our Institution (Bascom Palmer Eye Institute): Sengillo et al (2022)
   A. Demographics and baseline characteristics: 16 patients (18 eyes); 2.8 years of mean follow-up
   B. Functional and anatomic characteristics of patients with ARDs: 78% inferotemporal
   C. Long-term outcomes of nonsurgical management: 16 of 18 (89%) ARDs did not progress.
   D. Fellow eye pathology in patients with ARDs

IV. Conclusions
   A. Initial observational management can be considered for ARDs with no signs of progression.
   B. Surgical management remains the mainstay of symptomatic rhegmatogenous retinal detachments.
   C. Patient education and frequent follow-up after diagnosis are recommended.

Table 1. Outcomes of Asymptomatic Retinal Detachments With Initial Observational Management

Reference	No. of Patients	Outcomes	Comment
Jarrett (1988)[2]	16 (16 eyes)	16 eyes with delayed RD repair for various reasons, some asymptomatic 8 eyes underwent scleral buckling. 1 of 16 (6.3%) progressed to a macula-off detachment.	7 eyes demonstrated demarcation lines.
Brod et al (1995)[3]	28 (31 eyes)	29 of 31 (94%) remained asymptomatic. 2 (6.5%) underwent scleral buckling procedure.	Peripheral retinal pathology identified in 43% of fellow eyes
Byer (2001)[4]	17 (19 eyes)	2 of 18 (11%) progressed. 2 of 18 (11%) regressed.	Females (14 of 17 patients) were more likely to have subclinical retinal detachments.
Cohen (2005)[6]	16 (18 eyes)	All 18 eyes remained asymptomatic.	1 patient exhibited temporary progression that stabilized.
Shukla (2007)	17 (19 eyes)	1 of 19 (5.3%) required surgical intervention.	All patients received laser demarcation.
Lin et al (2019)	3 (3 eyes)	All 3 eyes remained asymptomatic.	All patients received laser demarcation.
Koçak et al (2019)	20 (21 eyes)	4 of 21 (19%) progressed to symptomatic retinal detachment.	All patients underwent laser demarcation. All eyes with progression had ≥3 D of myopia.

References

1. Schepens CL. Subclinical retinal detachments. *AMA Arch Ophthalmol*. 1952; 47:593-606.
2. Jarrett WH 2nd. Retinal detachment: is reparative surgery always mandatory? *Trans Am Ophthalmol Soc*. 1988; 86:307-320.
3. Brod RD, Flynn HW Jr, Lightman DA. Asymptomatic rhegmatogenous retinal detachment. *Arch Ophthalmol*. 1995; 113;1030-1032.
4. Byer NE. Subclinical retinal detachment resulting from asymptomatic retinal breaks: prognosis for progression and regression. *Ophthalmology* 2001; 108:1499-1503; discussion 1503-1494.
5. Byer NE. Spontaneous regression and disappearance of subclinical rhegmatogenous retinal detachment. *Am J Ophthalmol*. 2001; 131:269-270.
6. Cohen SM. Natural history of asymptomatic clinical retinal detachments. *Am J Ophthalmol*. 2005; 139;777-779.
7. Cheng AC, Yuen KS, Lam DS. Natural history of asymptomatic clinical retinal detachments. *Am J Ophthalmol*. 2005; 140:1170-1171; author reply, 1171.
8. Polkinghorne PJ. Natural history of asymptomatic clinical retinal detachments. *Am J Ophthalmol*. 2005; 140:1169; author reply, 1169-1170.
9. Ahmad N, West J. Current opinion on treatment of asymptomatic retinal detachments. *Eye (Lond)*. 2007; 21;1179-1185.

Update on the Management of Rhegmatogenous Retinal Detachment

Rajeev H Muni MD

The recent application of advanced multimodal imaging to assess outcomes following rhegmatogenous retinal detachment (RRD) has identified several anatomic biomarkers of "integrity". These include retinal vessel printings on fundus autofluorescence suggestive of retinal displacement, outer retinal folds, residual subretinal fluid blebs, and discontinuity and hyporeflectivity of the outer retinal bands (such as the ellipsoid zone and external limiting membrane) on en face and cross-sectional optical coherence tomography (OCT). Ultra-widefield swept-source OCT has expanded our understanding of retinopexy techniques. Time to surgery, choice of procedure and variations in techniques including method of subretinal fluid drainage, choice of tamponade and positioning all impact post-operative "integrity" of anatomic attachment. These findings have led to novel insights regarding the physiology of RRD and reattachment, structural changes to the foveola, and the pathophysiology of various post-operative anatomic abnormalities. This talk will provide an up to date summary of these recent findings and how they impact every aspect of RRD repair.

Floaterectomy: The Good, the Bad, and the Ugly

Jayanth Sridhar MD

I. Introduction

A. Visually significant floaters may reduce patient quality of life and result in patients seeking options for treatment.

B. The impact of floaters on patient quality of life may be more pronounced in the era of multifocal IOLs, in which reduced contrast sensitivity may result in patients being more symptomatic from floaters.

C. Treatment options for floaters in the absence of concomitant retinal pathology include observation, laser vitreolysis, and vitrectomy.

II. Benefits of Vitrectomy for Floaters

A. Multiple studies have demonstrated efficacy in vitrectomy in improving subjective visual quality and quality-of-life scores.

B. Surgery is technically simple and can be performed with multiple gauges.

C. Overall complication rate is low.

III. Risks of Vitrectomy for Floaters

A. Cataract formation

B. Not insignificant risk of retinal tear and detachment during or after surgery

C. Low but real risk of vision loss due to endophthalmitis and other rare complications of surgery

IV. Remaining Controversies in Care

A. Should a posterior vitreous detachment be induced intraoperatively?

B. What should be the extent of vitrectomy?

C. How best should the severity of vitreous floaters be captured in order to stratify patients to observation or treatment recommendation?

References

1. Schiff WM, Chang S, Mandava N, Barile GR. Pars plana vitrectomy for persistent, visually significant vitreous opacities. *Retina* 2000; 20(6):591-596.
2. Mossa F, Delaney YM, Rosen PH, Rahman R. Floaterectomy: combined phacoemulsification and deep anterior vitrectomy. *J Cataract Refract Surg.* 2002; 28(4):589e92.
3. Mura M, Engelbrecht LA, de Smet MD, Papadaki TG, van den Berg TJ, Tan HS. Surgery for floaters. *J Ophthalmol.* 2011; 118(9):1894-1894.e1.
4. Schulz-Key S, Carlsson JO, Crafoord S. Long term follow-up of pars plana vitrectomy for vitreous floaters: complications, outcomes and patient satisfaction. *Acta Ophthalmol.* 2011; 89(2):159-165.
5. Tan HS, Mura M, Lesnik Oberstein SY, Bijl HM. Safety of vitrectomy for floaters. *Am J Ophthalmol.* 2011; 151(6):995-998.
6. de Nie KF, Crama N, Tilanus MA, Klevering BJ, Boon CJ. Pars plana vitrectomy for disturbing primary vitreous floaters: clinical outcome and patient satisfaction. *Graefes Arch Clin Exp Ophthalmol.* 2013; 251:1373-1382.
7. Mason JO, Neimkin MG. Safety, efficacy, and quality of life following sutureless vitrectomy for symptomatic vitreous floaters. *Retina* 2014; 34:1055-1061.
8. Sebag J, Yee KM, Wa CA, Huang LC, Sadun AA. Vitrectomy for floaters: prospective efficacy analyses and retrospective safety profile. *Retina* 2014; 34(6):1062-1068.
9. Lin Z, Zhang R, Liang QH, et al. Surgical outcomes of 27-gauge pars plana vitrectomy for symptomatic vitreous floaters. *J Ophthalmol.* 2017; 2017:5496298.
10. Lam DS, Leung HY, Liu S, Radke N, Yuan Y, Lee VY. Two-port pars plana anterior and central core vitrectomy (Lam floaterectomy) in combination with phacoemulsification and intraocular lens implantation under topical anesthesia for patients with cataract and significant floaters: results of the first 50 consecutive cases. *Asia Pac J Ophthalmol (Phila).* 2017; 6(1):33-36.
11. Hahn U, Krummenauer F, Ludwig K. 23G pars plana vitrectomy for vitreal floaters: prospective assessment of subjective self-reported visual impairment and surgery-related risks during the course of treatment. *Graefes Arch Clin Exp Ophthalmol.* 2018; 256(6):1089-1099.
12. Zeydanli EO, Parolini B, Ozdek S, et al. Management of vitreous floaters: an international survey the European VitreoRetinal Society Floaters Study report. *Eye (Lond).* 2020; 34(5):825-834.
13. Waseem TC, DaBreo ER, Douglas J, et al. Pars plana vitrectomy for symptomatic vitreous floaters: another look. *Int J Ophthalmol Clin Res.* 2021; 8:124.
14. Delaney YM, Oyinloye A, Benjamin L. Nd:YAG vitreolysis and pars plana vitrectomy: surgical treatment for vitreous floaters. *Eye (Lond).* 2002; 16(1):21-26.

Vitreoretinal Surgery Panel

Panel Moderator: Gaurav K Shah MD

Panelists: Philip J Ferrone MD, Marta Figueroa MD, Raymond Iezzi MD, and Lejla Vajzovic MD

NOTES

When Should a Retina Specialist Offer a Minimally Proven Investigational Treatment?

Paul Sternberg Jr MD

I. What is a "minimally proven investigational treatment (MPIT)"?
   A. Procedures
      1. Limited clinical testing
      2. Lack of placebo or control study arm
      3. Absence of a clinical trial
   B. Drug or device
      1. No FDA approval
      2. Not approved for suggested indication

II. What would prompt consideration of an MPIT?
   A. Serious condition for which there are no approved therapies
   B. Serious condition for which approved therapies have not been effective
   C. Condition where new treatment appears markedly better than conventional treatment

III. What are the risks and concerns?
   A. Ethical
      1. Such patients are highly vulnerable.
      2. False hope
      3. Specialist could be lured by financial or marketing benefits, rather than best interest of patient.
   B. Patient safety
      1. Unknown risk profile
      2. Limited follow-up

IV. What are the benefits?

   Transformative patient care

V. So how do you make the decision about offering an MPIT?
   A. Is there a satisfactory alternative therapy available to diagnose, monitor, or treat the patient's disease or condition?
   B. How severe are the potential risks of the investigational therapy, and are those risks not reasonable in the context of the patient's disease or condition?
   C. Does the potential benefit to the patient justify the risks of the investigational therapy?
   D. Does the patient meet inclusion criteria for an existing clinical trial of the investigational therapy?
   E. Is the patient able to make an informed decision, and has the informed consent been obtained in an open and ethical manner?

The Future of In-Office Retinal Surgery

Tarek S Hassan MD

I. Questions Regarding Office-Based Surgery for Retina
   A. Is there a future?
      1. Asked for 25+ years
      2. Still no firm answer
   B. If yes . . .
      1. Is that future now, or later?
      2. What will such a future look like?
   C. If no . . . why not?

II. Questions have been asked before.
   A. 1985: United States allowed government (Medicare)-funded cataract extraction (CE) to be done as an outpatient procedure.
      1. Launched a new era: CE in ambulatory surgery centers (ASCs)
      2. Began a continuous push toward finding medically safe, lower-cost settings for surgical procedures
      3. Reimbursement schedules adjusted
      4. Concerns about this shift were similar to those today as CE tries to move to office-based settings.
         a. Safety, quality, ethics, etc.
         b. Solutions: Strict guidelines
            i. Strong commitment to enforced regulations
            ii. ASCs became high-quality, sophisticated, safe environments for patients and surgeons.
   B. Now: Same questions about moving CE and other eye surgery to OBS settings

III. Office-Based Surgery (OBS)
   A. Defined: Any surgical procedure performed by a licensed physician in the office setting that requires some level of anesthesia
   B. Future of OBS for CE and retina—Is it now?
      1. Capabilities exist, so . . . YES
      2. Hurdles to overcome exist, so . . . MAYBE
   C. OBS cataract and refractive surgery is being done in a few places around the globe.
      1. Safe success has been reported and published. Kaiser groups: Ianchulev T, et al. *Ophthalmology*. 2016;doi:10.1016/j.ophtha.2015.12.020.
         a. 21,501 eyes underwent CE in OBS settings.
         b. Good visual outcomes with acceptable safety profile
            i. Postop mean VA = 20/28
            ii. Surgical reintervention at 6 months = 0.7%
            iii. Low complication rate: 0.34% vitreous loss, 0 cases of endophthalmitis
         c. Study results may not be transferable to many/most OBS setups.
            i. Their sites had safety protocols not achievable in all outpatient settings and were able to more easily select most suitable patients given their greater system-wide scheduling flexibilities.
            ii. All sites had crash carts with stat teams always available to treat severe medical complications.
            iii. All OBS locations were within 1.5 km of a Kaiser hospital.
      2. Currently 50-100 OBS suites in the U.S. owned by ophthalmologists
   D. Only a minimal number of retina procedures are currently done in OBS settings.
   E. Numerous other specialties perform OBS procedures: gastroenterology, ENT, dermatology, cardiology, maxillofacial surgery, etc.

IV. Is it time for OBS for retina procedures and even more CE?
   A. Majority of all CE and retina surgery is done in ASCs.
   B. What has prevented the move to more OBS in ophthalmology?
      1. Numerous hurdles have derailed momentum among surgeons, industry, and payers.
      2. Hurdles in one arena generate more hurdles in others.

C. These hurdles can be overcome to move more surgery, particularly retina, into OBS settings by understanding and acting upon the things we want, the things we need, and the things we do not need.

1. For OBS, we want:
    a. Safety
    b. Efficacy
    c. Efficiency
    d. Compensation
    e. Overall improvement over the status quo
2. For OBS, we need:
    a. Change in mindset toward such a radical change
    b. Sterility
    c. Facilities (space)
    d. Equipment
    e. Patient management
    f. Reimbursement
3. For OBS, we do not need:
    a. Large capital investment
    b. Changing existing physical plant/facilities
    c. Large practice pattern changes
    d. Aggressive marketing
    e. Staffing changes
    f. Contractually binding consulting, contracting, and implementation services

D. Hurdles to office-based retinal surgery and potential solutions, including comparison to ASCs

1. Safety and regulatory oversight
    a. Overall: AMA guidelines

    OBS suites where surgery is done with moderate sedation or more for anesthesia should have accreditation of facilities by the same national organizations that accredit ASCs and hospital operating rooms.

        i. Standards for ASCs vary slightly but are similar in all 50 U.S. states.
            (a) Include surgical environment, ASC Life Safety Code, anesthesia, nursing, infection control, patient checklists and assessments, medical records, oversight and administration of drugs, etc.
            (b) CMS being urged to require same standards for OBS facilities, which are currently "allowed" in all 50 U.S. states (not generally affected by certificate of need requirements).
        ii. Increasing regulatory oversight of OBS in essentially every state—Federation of State Medical Boards: https://www.fsmb.org/siteassets/advocacy/key-issues/office-based-surgery.pdf

    b. Patient safety—systemic
        i. Most ophthalmologic procedures are not actually truly "routine."
            (a) Most patients are elderly and likely have comorbidities.
            (b) Ophthalmic Outpatient Surgery Society (OOSS) study (August 2015): http://ooss.org/wp-content/uploads/FINAL-2017-ASCRS-OOSS-SEE-ASC-Rule-Comments.pdf
                (i) Evaluated 170 ophthalmic ASCs—random samples of 50 recent CE cases
                - "Routine" cases are rare; 94% of CE patients had at least 1 comorbidity including HTN, heart disease, cerebral vascular disease, pulmonary disease, endocrine disease, and cancer.
                - Most take at least 1 prescription med for comorbidities.

                (ii) Virtually all cataract patients are at risk for significant medical complications.
            (c) Need for anesthesia services, MD or CRNA
                (i) Elderly patients with comorbidities
                (ii) Others who are not able to undergo local anesthesia—anxiety, claustrophobia, etc.; not always predictable
                (iii) Study: Significant number of cases needing anesthesia "intervention": Rosenfeld SI, et al. *Ophthalmology* 1999; 106(7):1256-1261.
                - 1006 CE patients
                - 37.4% required anesthesia intervention.
                - No preop characteristics predictive of need for intervention including pre-existing medical conditions, abnormal baseline EKG, sex, or age
        ii. 35 years ago, ASCs resembled the physician office procedure areas of today before they conformed to widespread safety standards.

c. Patient safety: ophthalmologic surgery
   i. Meeting surgical outcome goals; high likelihood in OBS settings
      (a) All equipment available
         (i) Cost is a factor; possibly rent or lease options?
         (ii) Smaller form factor such as new lasers, microscopes, and viewing systems exist or are coming in next versions of intraocular surgery machines
      (b) Likely all procedures possible with anesthesia services in OBS settings
      (c) Some not likely possible without anesthesia services
         (i) Scleral buckle procedures
         (ii) Significant orbital procedures
   ii. Meeting surgical sterility goals: high likelihood in OBS settings
      (a) Build full office surgical suite
         (i) Potentially expensive
         (ii) Requires significant space
            - Commitment to OBS is long-term with office modification
            - Can be built to meet ASC and hospital OR standards
      (b) Portable laminar flow units able to provide any office space with operating room sterility conditions
         (i) Devices reduce airborne bacteria and virus particles by up to 50x compared to levels in standard accredited hospital and ASC operating rooms.
            - Can likely create the utmost sterile conditions for surgery
            - Shown successful in a variety of studies of both simulated and actual operating room and OBS situations
         (ii) Larger units create full surgical suite sterile conditions.
         (iii) Smaller units create more local areas of sterility.
         (iv) Sometimes both used depending on size and scope of outpatient surgery
         (v) They can be moved in and out of office areas; offers flexibility to establish permanent or temporary options of having OBS available in existent office spaces.
         (vi) Inexpensive options relative to full-scale operating room buildout
         (vii) Currently used in more than 100 surgical settings in Europe and the Americas

2. Reimbursement issues
   a. Likely largest hurdle for significant uptake of OBS in retina and CE
   b. Unless OBS setting is a licensed ASC, it cannot collect a facility fee from government insurers and most carriers.
      i. A list of state-by-state OBS requirements: https://12uh.com/ioectr/state-by-state/
      ii. Billing must be done in the same way as office visits.
      iii. There is no reimbursement for office overhead.
   c. Some third-party payers will reimburse OBS procedures.
      i. Including a number of commercial plans and a few Medicare Advantage plans
      ii. Comprehensive straight Medicare coverage is rare.
   d. Professional fees are unaffected by the location of surgery.
      i. OBS professional fees are fully reimbursed.
      ii. OBS goal—negotiate a larger carve-out for procedures
         (a) "Enhanced professional fee" potentially possible
         (b) "Per-case" fee potentially possible
         (c) Demonstrate overall savings to carriers; no facility fee payment and potentially no anesthesia payment
   e. Overall: CMS and/or private insurer payments must cover practice expenses to make OBS successful.
      i. Creating fully equipped traditional surgical suites in the office environment is expensive for most practitioners.
      ii. Similar concerns existed with change of CE from inpatient to outpatient care years ago.
      iii. Currently, some surgeons fund OBS CE by only doing premium IOL cases.
         (a) Presently, a challenge for other specialties that do not currently have patient self-pay options
         (b) Opportunity to create potential new self-pay markets

V. OBS: Where are we going?
   A. There is an expanding future in ophthalmology.
      1. OBS for retina and CE is definitely possible, but the path toward widespread uptake is not easy.
      2. Hurdles must be overcome.
         a. Change in mindset among surgeons, patients, and payers
            i. Overcoming resistance to changing the status quo
            ii. Being willing to evolve and disrupt/change current practice patterns and patient flows
         b. Financial
            i. Startup costs
               (a) More expensive to build out full surgical suites vs. less expensive to utilize portable equipment to more flexibly create temporary surgical suites
               (b) Equipment: rent vs. lease vs. buy
               (c) Maintenance costs: stocking supplies, equipment maintenance, employees, etc.
            ii. Reimbursement
               (a) Understand and manage billing issues
               (b) Strategically negotiate with payers
                  (i) Strategy should pointedly emphasize cost savings in OBS setting.
                  (ii) Best done by practices working directly with proper people at the carrier; no need to hire contracted fee-based companies to effectively negotiate reimbursement
                     - Enhanced professional fees
                     - Potentially some facility fee payments
               (c) Revenue cycle management and inventory management can be done by existing office staff or service with some training
         c. Procedural
            i. Space
               (a) Build out permanent surgical suites vs. utilize existing spaces with temporary portable surgery suite solutions
               (b) Consider cost and permanence
            ii. Anesthesia services
               (a) Full-time vs. part-time
               (b) Reimbursement issues for anesthesia providers
            iii. Surgical staff training: by physician, industry, consultants
            iv. Practice building: advertising, referral marketing, etc.
         d. Overcome the false narrative that a fee-based consultant service is needed to begin OBS
            i. Pathway to implementing OBS in retina and cataract practice is straightforward albeit somewhat laborious.
            ii. Physician, industry, and per diem for-hire consultant services can assist implementation without binding physician reimbursement to long-term outside management fees.
            iii. Reliance on outside firms to establish OBS in clinical practice is ultimately an obstacle to continued expansion of OBS in retina and ophthalmology as most practices will not utilize such services.
   B. OBS for retinal surgery
      1. It is possible for nearly all indications (even scleral buckle if anesthesia support is present).
      2. Hurdles must be overcome to obtain reliable reimbursement from government insurers, and to a lesser extent, private payers.
      3. Economics of performing retina surgery must be considered relative to following the current path of least resistance—operating in an efficient ASC.
      4. More options exist for office-based surgical suite creation, procurement and upkeep of equipment, and hiring and/or outsourcing surgical suite employees.
      5. Retina OBS can begin soon, and potentially flourish, with new and expanding retina indications.
         a. Sustained-release anti-VEGF implants (PDS)
         b. Vitreous floaters (insurer and self-pay)
      6. May be beneficial to patient, surgeon, and health-care system overall if efficiently and safely employed

Medical Moneyball? The Benefits and Pitfalls of Private Equity Retina Practice Consolidation

John T Thompson MD

I. The Basics

A. Private equity (PE) purchases of ophthalmology and optometry practices have increased over the past 5 years, with little slowdown during the height of the COVID-19 pandemic. A total of 245 PE acquisitions occurred between 10/21/19 and 9/1/21 from 30 different PE companies.[1]

B. Most private retina specialists have received at least a few email or phone queries from a PE company interested in their practice. Those who have not already sold want to understand better the process for PE acquisition of retina practices and potential implications if they do decide to be acquired by one.

C. There are 2 basic models for PE purchases in ophthalmology:

1. Vertical integration of primary ophthalmology, optometry, subspecialists under one umbrella and
2. Horizontal integration of retina-only practices spread throughout the United States

D. What does the PE company purchase?

1. The PE company does not "buy" your medical practice, but you give their management services organization (MSO) a contract to take over managing your practice.
2. Practice owners are selling a percentage of their profit in perpetuity (often 40%-60%) to the MSO for an up-front payment and possibly some stock in the MSO. The MSO has a controlling interest in the practice even if the retina specialist does not sell over 50% of their profit.

E. What is the process for a PE sale?

1. The interested group must have internal discussions and then hire advisors (typically an attorney and investment banker) to evaluate their practice.
2. The practice is marketed to potential suitors with the goal of finding a philosophical fit at the highest price. Your investment banker helps to maximize your attractiveness to the PE firm.
3. Once the most promising PE company is selected, you must sign a nondisclosure agreement and letter of intent giving a 90-120 day commitment to not talk to other PE firms.
4. Much more extensive due diligence then starts: the practice quality of earnings is evaluated, leading to calculation of the earnings before interest taxes, depreciation, and amortization (EBITDA). This is the financial world's method of determining your practice profitability. An adjusted EBITDA is calculated to exclude nonrecurring expenses or profits.
5. If favorable, the next step is negotiating a final agreement, including a purchase agreement, noncompete agreement, employment agreement, and lease/real estate agreements. Your lawyer is paid by the hour, and costs will likely exceed $100,000, depending on the size of your practice. The investment bank receives a percentage of the total sale (2%-5% and perhaps higher if they get a premium price for you). Your business manager and the partners will spend many, many hours in conferences during this phase.
6. If everything is agreed, then the PE firm pays a multiple of adjusted EBITDA upon closing; this can be negotiated to be all cash or a combination of cash and some stock (perhaps 20% of purchase price) in the PE MSO (more common now). Almost all is taxed a long-term capital gain rate, which is historically low (20% + 3.8%).
7. The PE MSO manages your practice with the goal of making it more profitable.
8. It plans to sell your practice to another potentially larger entity ("the second bite") in 5-7 years at another multiple (3-5x EBITDA); the profit to be returned to PE investors.

F. What makes a practice attractive for PE purchase?

1. PE companies typically use a hub-and-spoke model with the goal of acquiring a larger group in the region as the hub and later absorbing smaller groups as the spokes.
2. Larger groups with a good geographic footprint, high productivity, excellent profitability, ownership of surgicenters, and a good prospect for growth are most attractive as hubs and command a premium price, often receiving 10-12x adjusted EBITDA for their sale to the MSO. Smaller spoke practices are important in their growth strategy for taking over a region, but usually receive only 5-6x EBITDA. This is true even though the smaller practices have more potential gain in profitability to the PE firm by joining a much larger group due to volume discounts for pharmaceuticals, outsourcing administrative functions to the larger group, and other consolidation-related cost savings.

II. Should you consider a PE buyout of your retina practice? The Good and the Bad

A. The good

1. Medical reimbursements have dropped substantially in retina over the past 15 years, and the future of physician reimbursement is uncertain. A multimillion dollar check invested intelligently now is a sure thing and can serve as a hedge against declining physician income.
2. Running a practice, like running any relatively small business, is difficult, with the challenges of hiring/firing staff, managing human resources, complying with increasing governmental/insurer regulations, investing money to grow the practice or modernize equipment, managing disagreements among physician partners, and finding new physician associates. After a buyout this is no longer your problem, as the MBAs from the MSO will handle this for you. You will have to serve on some committees, but long partner meetings become a thing of the past.

B. The bad

1. You are no longer in control of your practice. This is a huge change for partners who created their practices decades ago. There is a "honeymoon" phase in the first 1-2 years after purchase, but the reality of being an employed MD with little power sets in as the PE firm pushes to make the practice more profitable.
2. It is very difficult to measure quality but easy to measure dollars and cents, so your productivity will be monitored constantly.

   The only way to improve the practice profitability to get the maximum payout for the second bite is to increase revenue or decrease expenses. They can increase revenue by having you see more patients, order more procedures, or bill more aggressively. Decreased expenses can be achieved relatively painlessly to some degree with larger volume discounts for pharmaceuticals and services for the aggregated practices, but the MSO will likely also look to decrease staff salaries by attrition, decrease staff benefits, outsource billing to a central office, share an administrator between several practices, and use many other methods to try to minimize their costs.
3. Staff morale will suffer; they all know you got millions and they got peanuts.
4. If you are unhappy your only option is to leave, but restrictive covenants are formidable.

III. My Predictions

PE buyouts are attractive to practice owners nearing the end of their career and pessimists who think MD salaries are headed downhill. It is a bigger risk for young and mid-career MDs. There will be increased physician turnover and less joy in the practice of retina. Most will fail to achieve projected increased value in the second bite, but a few will succeed.

Reference

1. Patil SA, Vail DG, Cox JT, et al. Private equity acquisition in ophthalmology and optometry: a time series analysis of the pre-COVID, COVID pre-vaccine, and COVID post-vaccine eras. MedRxiv preprint, available at: https://doi.org/10.1101/2022.02.03.22270390.

The Health Policy Implications of Biosimilars

George A Williams MD

Definition of Biosimilars

Biological products, or biologics, are large complex molecules made from living sources such as bacteria, yeast, and animal cells.[1] Biologics are the fastest growing class of medications in the United States and are among the most effective and expensive drugs available. They account for 2% of prescriptions but 37% of net spending on prescriptions.[2] In 2009, the Food and Drug Administration (FDA) created an abbreviated approval pathway for biological products that are demonstrated to be similar to or interchangeable with FDA-approved biological products. Such biological products are termed "biosimilars." The biosimilar approval pathway was formed with the goals of improved patient access, increased treatment options, and potentially lower treatment costs.[3]

During the approval process, biosimilars are directly compared to an original FDA-approved biologic termed the "reference product." The reference product had been approved in a separate application demonstrating safety and efficacy. The purpose of the biosimilar development program is to demonstrate similarity between the biosimilar and the reference product, not to independently establish the safety and efficacy of the proposed biosimilar. However, this pathway involves an extensive structural and functional comparison to the reference product to establish that the biosimilar has no clinically meaningful differences when compared with the reference product in terms of safety, purity, and potency for the labeled indications. Biosimilars are identified by adding a 4-letter suffix to the name of the reference product.

Biosimilars in Ophthalmology

The FDA approval and availability in 2022 of ranibizumab-nuna for some indications of ranibizumab has substantial implications for retinal drug therapy involving step therapy and compounded bevacizumab access.[4] Additionally, aflibercept biosimilars are under development, as well as a bevacizumab biosimilar (bevacizumab-vikg) with FDA-approved ocular indications.

Impact of Biosimilars on Step Therapy

Step therapy policies are likely to be affected by biosimilars. According to the Kaiser Family Foundation, step therapy, or "fail first" therapy, for Part B drugs is now present in 98% of Medicare Advantage plans, covering nearly 40% of Medicare beneficiaries.[5] Typically, step therapy in Medicare Advantage requires patients be treated with compounded bevacizumab before approval of treatment with brand name drugs with FDA-approved indications. Unfortunately, the criteria for treatment failure are variable and arbitrary between different Medicare Advantage plans, creating an administrative burden for practices. Although compounded bevacizumab is an effective treatment for many patients, the Academy believes that the choice of drug treatment should be a shared decision between the patient and their physician after a thorough discussion of the risks and benefits of each treatment and not determined by insurance companies.

How Medicare Advantage plans and other insurers will integrate biosimilars into step therapy protocols remains uncertain, but the initial experience with bevacizumab biosimilars is concerning. Currently, there are two FDA-approved bevacizumab biosimilars: bevacizumab-awwb and bevacizumab-bcvr. Upon approval, multiple insurance companies included these biosimilars into their ophthalmologic step therapy protocols, even though neither biosimilar had been studied in the eye and both contained potentially toxic excipients when injected into the eye. Fortunately, after the Academy contacted the Centers for Medicare and Medicaid Services, pointing out that these biosimilars were not approved for ophthalmic indications, permission to use these biosimilars in ocular disease was revoked, but the potential for use of ocular biosimilars in step therapy was confirmed.[6]

Compounded Bevacizumab Access

Compounded bevacizumab remains the most administered intravitreal medication in the U.S.[7] Use of bevacizumab has saved billions of dollars compared to brand name drugs since 2006. A bevacizumab biosimilar, bevacizumab-vikg, has completed clinical trials for ocular indications and will soon be submitted to the FDA for possible approval. Although this drug is a biosimilar, it will not be treated as other biosimilars because there are no FDA-approved ocular indications for bevacizumab. It will therefore be submitted for review as a novel drug in the normal biologic licensing pathway. This will eliminate some of the concerns about the contamination risks, formulation, and consistency of compounded bevacizumab. However, if it is approved, such approval for ocular disease may affect access to compounded bevacizumab. It is FDA policy that if there is an FDA-approved drug, the same drug cannot be compounded for the same indication.[4] Since compounded bevacizumab is used in approximately 40% of intravitreal injections, there are concerns about the adequacy of supplies and increased cost of bevacizumab-vikg compared with compounded bevacizumab.

References

1. FDA. Overview of biosimilar products. www.fda.gov/media/151058/download.
2. Mulcahy A, Buttorff C, Finegold K, et al. Projected US Savings from biosimilars, 2021-2025. *Am J Manag Care*. 2022; 28(7).
3. FDA. Biosimilar regulatory review and approval. www.fda.gov/media/151061/download.
4. Williams GA, Glasser DB, Repka MX. The promise and perils of biosimilars in ophthalmology. *Ophthalmol Retina*. 2022; 6(7):537-539.

5. Freed M, Damico A, Neuman T. A dozen facts about Medicare Advantage in 2020. KFF website. www.kff.org/medicare/issue-brief/a-dozen-facts-about-medicare-advantage-in-2020/. Jan. 13, 2021.
6. Zirabev, Mvasi may not be used to treat eye disease, CMS says. AAO Eye on Advocacy website. https://www.aao.org/eye-on-advocacy-article/cms-responds-to-our-call-zirabev-mvasi-may-not-be. Nov. 9, 2021.
7. Glasser DB, Parikh R, Lum F, Williams GA. Intravitreal anti-vascular endothelial growth factor cost savings achievable with increased bevacizumab reimbursement and use. *Ophthalmology* 2020; 127;1688-1692.

Unconscious Gender Bias—What Is It, Where Are We At?

Tanya Trinh MBBS

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In These Unprecedented Times . . .

2022 Retina Subspecialty Day

Sohail J Hasan MD PhD

Action Requested: Support Ophthalmology's Advocacy Efforts

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. Be part of the community that ensures ophthalmology has a strong voice in advocating for patients.

Where and How to Invest

During AAO 2022 in Chicago, invest in OPHTHPAC and Surgical Scope Fund at either of our two convention center booths (in the Grand Concourse and Lakeside Center) or online. You may also invest via phone by texting **MDEYE** to **41444** for **OPHTHPAC** and texting **SCOPE** to **51555** for the Surgical Scope Fund.

We also encourage you to support our congressional champions by making a personal investment to their re-election campaign via OPHTHPAC Direct, a unique and award-winning program that lets *you decide* who receives your political support.

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.

Why Invest?

Academy Surgical Scope Fund contributions are used to support the infrastructure necessary in state legislative/regulatory battles and for public education. OPHTHPAC investments are necessary at the federal level to help elect officials who will support the interests of our profession and our patients. Similarly, state Eye PAC contributions help elect officials who will support the interests of our patients at the state level. Contributions to EACH of these three funds are necessary and help us protect sight and empower lives.

Protecting quality patient eye care and high surgical standards is a "must" for everybody. 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 thrive and patients receive optimal care.

OPHTHPAC for Federal Advocacy

OPHTHPAC is the Academy's award-winning nonpartisan political action committee, representing ophthalmology on Capitol Hill. OPHTHPAC works to build invaluable relationships with our federal lawmakers to garner their support on issues such as:

- Improving the Medicare payment system, so ophthalmologists are fairly compensated for their services
- Securing payment equity for postoperative visits, which will increase global surgical payments
- Stopping optometry from obtaining surgical laser privileges in the veterans' health-care system
- Reducing prior authorization and step therapy burdens

Academy member support of OPHTHPAC makes all this possible. Your support provides OPHTHPAC with the resources needed to engage and educate Congress on our issues, helping advance ophthalmology's federal priorities. Your support also ensures that we have a voice in helping shape the policies and regulations governing the care we provide. Academy member support of OPHTHPAC is the driving factor behind our advocacy push, and in this critical election year, we ask that you get engaged to help strengthen our efforts.

At the Academy's annual Mid-Year Forum, the Academy, 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. As part of this year's meeting, these three societies each supported participation of fellowship trainees via the Academy's Advocacy Ambassador Program. During Congressional Advocacy Day, they visited members of Congress and their key health-care staff—either in person or virtually—to discuss ophthalmology priorities. The three retina societies remain crucial partners with the Academy in its ongoing federal and state advocacy initiatives.

Surgical Scope Fund for State Advocacy

The Surgical Scope Fund (SSF) provides grants to state ophthalmology societies in support of their efforts to protect patient safety from dangerous optometric surgery proposals. Since its inception, the Surgery by Surgeons campaign and the SSF, in partnership with state ophthalmology societies, have helped 43 state/territorial ophthalmology societies reject optometric scope of practice expansions into surgery.

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

Dollars from the SSF are critical to build complete cutting-edge political campaigns, including media (TV, radio, and social media), educating and building relationships with legislators, and educating the voting public to contact their legislators. This helps to preserve high surgical standards 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 to fight for patient safety.

The Academy's Secretariat for State Affairs thanks the ASRS, the Macula Society, and the Retina Society, which have joined state ophthalmology societies in the past in contributing to the SSF, and looks forward to their 2022 contributions. These ophthalmic organizations complete the necessary SSF support structure for the protection of our patients' sight.

Surgical Scope Fund	OPHTHPAC®	State Eye PAC
To protect patient safety by defeating optometric surgical scope-of-practice initiatives that threaten quality surgical care	Support for candidates for U.S. Congress	Support for candidates for state House, Senate, and governor
Political grassroots activities, government relations, PR and media campaigns No funds may be used for campaign contributions or PACs.	Campaign contributions, legislative education	Campaign contributions, legislative education
Contributions: Unlimited Individual, practice, corporate, and organization	Contributions: Personal contributions are limited to $5,000. Corporate contributions are confidential.	Contribution limits vary based on state regulations.
Contributions are 100% confidential.	Personal contributions of $199 or less and all corporate contributions are confidential. Personal contributions of $200 and above are on the public record.	Contributions are on the public record depending upon state statutes.

State Eye PAC

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 fought on the state level.

Support Your Colleagues Who Are Working on Your Behalf

Two Academy committees made up of your ophthalmology colleagues are working hard on your behalf. 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 used to protect Surgery by Surgeons during scope battles at the state level.

OPHTHPAC Committee

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Rediscovering AMD With Swept Source OCT Imaging

Philip J Rosenfeld MD PhD

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My Best Medical Retina Case

William F Mieler MD, Anita Agarwal MD, Amani Fawzi MD, Jose S Pulido MD MS, and Lihteh Wu MD

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What's New in Retinal Degenerations?

Jacque L Duncan MD

Retinal dystrophies and degenerations represent one of the most exciting frontiers in ophthalmology. They are among the most challenging diseases that ophthalmologists encounter because they are exceptionally heterogeneous: each broad diagnostic category, like retinitis pigmentosa, results from disease-causing variations in almost 90 distinct genes and likely represents at least as many different diseases. Autosomal dominant, autosomal recessive, X-linked, and mitochondrial inheritance have all been reported for nonsyndromic retinal degenerations, and many cases are associated with systemic manifestations. Many retinal specialists are not familiar with how to interpret the tests used to characterize retinal degenerations, including genetic, psychophysical, and electrophysiological testing, making it challenging to accurately characterize and diagnose patients. The range of diseases can be overwhelming, and traditionally there have been limited-to-no treatments for retinal degenerations.

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] More widespread use of genetic testing requires retinal specialists and ophthalmologists to understand how to interpret genetic test results. In most cases, explanation of genetic test results is best done in partnership with a genetic counselor who can help interpret results that are often complicated by variants of uncertain significance and that may be disease-causing but have not been reported in other patients. As genetic testing becomes more widespread, variants can be reclassified as likely pathogenic or likely benign, and initiatives such as the Clinical Genome Resource, or ClinGen (https://clinicalgenome.org/), have been founded to define the role of genetic variants in disease. Genetic testing and genetic counseling should be provided for patients with inherited retinal degenerations and is 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 discovery of new genes associated with retinal degenerations.

Genetic testing became clinically important for patients with early-onset retinal degenerations beginning 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] The first gene-specific therapy approved for treatment of human disease, it stimulated many clinical trials of gene-based therapies for diseases including achromatopsia, choroideremia, X-linked retinoschisis, X-linked retinitis pigmentosa, and even AMD. In the past year, several of these trials reported promising results, but many failed to meet the prespecified endpoint of the primary outcome measure for the clinical trial, including trials of gene augmentation for *CHM*, *RPGR*, and *CEP290*. The results demonstrate the critical importance of clinical trial design based on information from well-designed natural history studies and communication with regulatory agencies such that the study is designed to demonstrate significant change in the specified primary outcome measure. Furthermore, long-term results are becoming available at greater than 3 years after FDA approval of voretigene neparvovec, demonstrating sustained visual benefit to most patients.[4] However, some patients develop chorioretinal atrophy in the posterior pole, not always related to the region where the treatment was delivered.[5] The impact on patient visual function and the mechanism for this finding are not clearly understood.

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, including antisense oligonucleotide therapies, were developed for large genes with common variants that introduce splicing defects in genes including *CEP290* and *USH2A*.[6] Gene editing with clustered regularly interspaced short palindromic repeats (CRISPR) may offer a new approach for genes that exceed the carrying capacity of AAV or for autosomal dominant retinal degenerations. The first use of CRISPR to treat a patient at the site of the disease was reported for patients with *CEP290*-related retinal degeneration and demonstrated early evidence of safety in September 2021; studies are ongoing to assess treatment effect on visual function.

Gene-specific therapies could slow vision loss or improve vision of photoreceptors that have not degenerated. However, for patients who do not have identified variants in genes known to cause retinal degeneration, treatments that intervene in pathways that cause retinal degeneration may prevent photoreceptor degeneration[7] or reduce oxidative stress to photoreceptor survival and improve visual function.[8] For patients with advanced disease, therapies including prosthetic devices may use electrical stimulation of remaining cells to elicit some vision.[9,10] Gene therapy can introduce light-sensitive proteins that make non-photoreceptors respond to light through optogenetics, with partial restoration of sight to patients with profound vision loss from retinitis pigmentosa;[11] many other approaches are in clinical or preclinical development.[12]

In summary, retinal specialists need to stay informed about new developments and opportunities to care for their patients with retinal degenerations, perhaps the most promising areas of unmet need in ophthalmology.

References

1. RetNet, Retinal Information Network. https://sph.uth.tmc.edu/RetNet/. 2021.
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. 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.
5. Gange WS, Sisk RA, Besirli CG, et al. Perifoveal chorioretinal atrophy after subretinal voretigene neparvovec-rzyl for RPE65-mediated Leber congenital amaurosis. *Ophthalmol Retina*. 2022; 6(1):58-64.
6. 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.
7. 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.
8. 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.
9. 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*. 2021; 99(7):e1212-e1221.
10. 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.
11. Sahel JA, Boulanger-Scemama E, Pagot C, et al. Partial recovery of visual function in a blind patient after optogenetic therapy. *Nat Med*. 2021; 27(7):1223-1229.
12. 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.

Mimickers of AMD Every Ophthalmologist Should Know

Elliott Sohn MD

I. Essential Characteristics of AMD
   A. Clinical presentation including demographics, race, age
   B. Other factors that increase risk for AMD include genetics and smoking.
   C. There are mimickers for exudative and/or nonexudative AMD.

II. Value of Multimodal Imaging Including OCT and Autofluorescence

III. Importance of Past Medical History, Medications, and Family History

IV. Mimickers of AMD
   A. Macular dystrophies caused by genetic mutation. Need to inquire about family history. Age of onset typically younger than 50-60 years. Many of these have a distinct phenotype, some look just like AMD.
      1. Pattern dystrophy
         a. *PRPH2/RDS* mutation, autosomal dominant [AD] inheritance
         b. Central, relatively small vitelliform lesions
         c. Can result in atrophy and choroidal neovascularization (CNV)
      2. Best macular dystrophy
         a. *Best1/VMD2* mutation, AD inheritance
         b. Also autosomal recessive [AR] bestrophinopathy
         c. Relatively larger vitelliform lesions in the macula
         d. Often hyperopic with decreased axial length
      3. Stargardt disease
         a. *ABCA4* mutation, AR inheritance
         b. Flecks are more elongated and angled compared to drusen.
         c. Bull's eye maculopathy and atrophy in central macula
      4. *PROM-1* associated macular dystrophy
         a. AD inheritance
         b. Results in macular geographic atrophy (GA) and/or bull's eye maculopathy
      5. Stargardt-like dominant macular dystrophy: *ELOVL4* mutation, AD inheritance
      6. Maternally inherited diabetes and deafness
         a. Mitochondrial inheritance, A3243G transition
         b. Results in retinal pigment epithelial (RPE) changes, GA, sometimes multifocal, in the macula
      7. Macular disease from *IMPG1/IMPG2* mutation: Vitelliform lesions in the macula
      8. North Carolina Macular Dystrophy
         a. *IRX1/PRDM13* mutation, AD inheritance
         b. Can present with just drusen
         c. Typically static
   B. Medications that can be associated with fundus features mimicking AMD
      1. Pentosan polysulfate sodium (PPS, Elmiron)
         a. Inquire about history of interstitial cystitis ("bladder pain syndrome"), especially affecting women starting in their 40s
         b. Can occur as soon as a few years of being on PPS
         c. Risk is dose dependent, typically over 1-1.5 g cumulative dose.
         d. Has subretinal drusenoid deposits and often more prominent autofluorescence changes around nerve than seen in AMD
      2. Hydroxychloroquine (Plaquenil)
      3. Deferoxamine
   C. Posterior segment disorders
      1. Can cause CNV, including high myopia and angioid streaks. (Pseudoxanthoma elasticum is caused by mutation in *ABCC6*.)
      2. Could also include uveitic disorders such as punctate inner choroidopathy, but this is more common in relatively younger women
   D. Central serous chorioretinopathy
      1. Overlay with CNV but often results in bilateral RPE changes
      2. Consider age, but RPE abnormalities and history of choroidal vascular disease increase risk for CNV at an older age

E. MacTel type 2

1. Has degenerative component that can result in outer retinal atrophy but can also result in CNV
2. Typically presents at a younger age than AMD and has pathognomonic findings on fundus autofluorescence and OCT

F. Drusen and subretinal drusenoid deposits (SDDs, aka reticular pseudodrusen): Features of multiple disorders above

1. SDDs can be seen in AMD and PPS maculopathy and after acute hypertensive episodes such as in pre-eclampsia.
2. Other macular dystrophies that exhibit drusen
   a. Autosomal dominant radial drusen (aka Malattia Leventinese and Doyne honeycomb retinal dystrophy caused by *fibulin-3/EFEMP-1* mutation)
   b. Sorsby fundus dystrophy, resulting in bilateral CNV before the sixth decade of life caused by AR mutation in *TIMP-3*

Selected Readings

1. Han IC, Mullins RF, Stone EM, Sohn EH. Macular dystrophies. In: Sadda S, Schachat A, Wilkinson C, et al., eds. *Ryan's Retina*. 7th ed. Elsevier; 2022.
2. Mukhopadhyay C, Boyce TM, Gehrs KM, et al. Age-related macular degeneration masquerade: a review of pentosan polysulfate maculopathy and implications for clinical practice. *Asia Pac J Ophthalmol*. 2022; 11(2):100-110.

Noncancerous Masquerades

Phoebe Lin MD PhD

Introduction

In the medical and surgical fields, specialization has resulted in siloed areas of expertise that may sometimes fail to take the whole patient into account. Furthermore, in each medical specialty, particularly in ophthalmology, there has been further subspecialization. Within the retina subspecialty alone, this has occurred in a significant way, with inherited retinal disease experts, medical vs. surgical retina specialists, uveitis specialists, medical vs. surgical oncologists, and pediatric retina specialists, all somewhat siloed in their respective areas.

Background Observations

While benefits to patients occur when expertise is consolidated around a particular rare disease, this separation of expertise can occasionally result in a gap in knowledge for diagnoses that might present very heterogeneously or with overlapping characteristics of disparate disease entities. This can result in delay in diagnosis and management for sight-threatening and, potentially, life-threatening conditions and, at the very least, contributes significantly to patient distress surrounding medical uncertainty. Raising awareness of these scenarios can hopefully mitigate the consequences for our patients. Improving cross-subspecialty collaboration and coordination is also paramount in this effort. This talk will cover a number of cases that were subject to referral bias, eventually requiring multidisciplinary teams to coordinate treatment, and will ultimately provide a starting point to move toward improving patient care.

Selected Readings

1. Miller JML, Chang E, Besirli CG, Johnson MW, Demirci H. A novel OCT signature in leukemic papillopathy masquerading as autoimmune or infectious uveitis. *Graefes Arch Clin Exp Ophthalmol*. 2021; 259(5):1315-1322.
2. Rothova A, Ooijman F, Kerkhoff F, Van Der Lelij A, Lokhorst HM. Uveitis masquerade syndromes. *Ophthalmology* 2001; 108(2):386-399.
3. Micieli J, Micieli A, Schlenker MB, Kertes PJ. Growth of medical and surgical vitreoretinal subspecialization in Ontario over 12 years. *Can J Ophthalmol*. 2014; 49(4):312-319.

Ultrawide-Field Angiography in Retinal Vein Occlusion: SCORE2 Experience

Barbara Blodi MD

I. Use of Ultrawide-Field Fluorescein Angiography (UWF FA) in the SCORE2 Trial

A. SCORE2 was an NEI-sponsored randomized clinical trial that demonstrated noninferiority of aflibercept vs. bevacizumab in improving visual acuity in central retinal and hemiretinal vein occlusion (CRVO/HRVO) patients with macular edema. All eyes were treated with either aflibercept or bevacizumab monthly for 6 months and rerandomized to monthly vs. treat-and-extend through Year 1. Yearly follow-up visits through Year 5 were done off of the treatment protocol.[1]

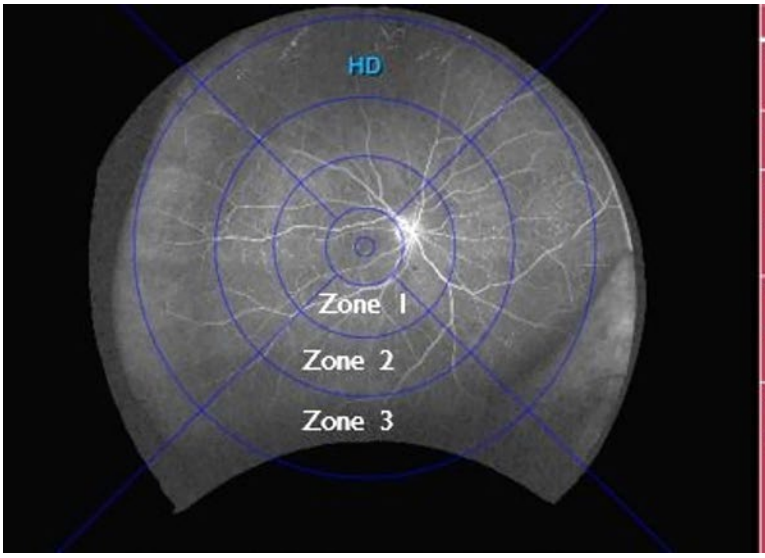
B. As a secondary outcome, investigators were interested in studying long-term UWF FA changes in both retinal leakage and retinal nonperfusion in eyes with CRVO/HRVO treated with anti-VEGF injections.

C. Investigators were given the opportunity to participate in a voluntary ancillary study of UWF FA. In 2014, at the start of the SCORE2 trial, the use of UWF imaging was not in widespread clinical use. Investigators enrolled 92 participants who underwent UWF FA at 7 visits: baseline, 6 months, and yearly for 5 years.

II. SCORE2 UWF FA Methods

A. All UWF FA participants were imaged on Optos TX (Optos PLC; Dunfermline, Scotland), with steered images to improve superior and inferior view. Grading was performed at Wisconsin Reading Center using the NetwORC (Network of Ophthalmic Reading Centres) grid (see Figure 1) shown below[2]; area measurements were done by planimetry and were corrected for peripheral warping. Image quality was assessed within each of the 14 NetwORC zones.[3]

B. Across all UWF FA imaging analyses there was no significant difference between the 2 anti-VEGF treatment groups; as a result, we have merged the results from both treatment groups.



Retinal Area	Definition
Fovea (Central 1 DA)	A circle centered on the fovea with a diameter of 1.8mm (1800 microns)
Macula (ETDRS grid)	A circle centered on the fovea with a diameter of 7.2mm. Equivalent to the ETDRS grid
Zone 1 (Inner periphery)	Ring between the outer border of the macula area and the border of Zone 2, with a width of 4.5mm
Zone 2 (Mid periphery)	Ring between the outer border of Zone 1, the inner periphery and the border of Zone 3, with a width of 4.5mm
Zone 3 (Outer periphery)	Ring between the outer border of Zone 2, the mid periphery, and the presumed border of retinal perfusion (outside border of Networc grid) with a width of 4.9mm

Figure 1. NetwORC grid. Total area within the NetwORC grid is 860 mm^2.

Table 1. Leakage Within the NetwORC Grid

	Baseline	Month 6	Year 1	Year 2	Year 3	Year 4	Year 5
Number of patients with gradable leakage	82/82 (100%)	66/80 (83%)	59/72 (82%)	48/53 (91%)	36/42 (86%)	25/31 (81%)	22/26 (85%)
Area of leakage (total area within the NetwORC grid = 860 mm^2)	289 mm^2 (34%)	62 mm^2 (7%)	69 mm2 (8%)	85 mm^2 (10%)	65 mm^2 (8%)	35 mm^2 (4%)	56 mm^2 (7%)

Table 2. Nonperfusion Within the NetwORC Grid

	Baseline	Month 6	Year 1	Year 2	Year 3	Year 4	Year 5
Number of patients with gradable nonperfusion	50/78 (64%)	62/78 (79%)	56/73 (77%)	47/54 (87%)	32/41 (78%)	23/31 (74%)	16/21 (76%)
Area of nonperfusion (total area within the NetwORC grid = 860 mm^2)	43 mm^2 (5%)	67 mm^2 (8%)	70 mm^2 (8%)	73 mm^2 (8%)	88 mm^2 (10%)	54 mm^2 (6%)	56 mm^2 (7%)

III. Leakage in SCORE2 Eyes With CRVO/HRVO

TOPLINE results: The data show that over 80% of participants continue to have some leakage over 5 years. Mean leakage area at baseline is one-third of the retina within the UWF grid. Leakage area decreases significantly from baseline to Month 6. Over the 5 years of follow-up, leakage does not completely resolve but remains at less than 10% involvement.

IV. Nonperfusion in SCORE2 Eyes With CRVO/HRVO

TOPLINE results: The data show that nonperfusion is present in 60% or more of SCORE2 participants at baseline. The percent involvement does not change significantly over 5 years (although loss to follow-up is significant in Years 3, 4, and 5). Mapping of nonperfusion from each subfield of Zones 1, 2, and 3 revealed that the temporal subfield in each zone had the highest percent involvement (data not shown).

V. Summary

A. In the subset of SCORE2 eyes with UWF FA, all patients had retinal leakage at baseline. Within the NetwORC grid, planimetry showed that 34% of the total retinal area was leaking at baseline. After 6 monthly injections with anti-VEGF treatment, retinal leakage decreased to <10% of total retinal area.

B. At baseline, UWF FA revealed nonperfusion in a majority of patients. The total retinal area of nonperfusion increased from 5% at baseline to 8% at Month 6 after 6 monthly injections; subsequent visits showed no significant change in area of nonperfusion.

C. SCORE2 data on correlation of leakage and nonperfusion to visual acuity will be shown at AAO 2022.

References

1. Scott IU, VanVeldhuisen PC, Oden NL, Ip MS, Blodi BA; SCORE2 Investigator Group. Month 60 outcomes after treatment initiation with anti-VEGF therapy for macular edema due to central or hemi-retinal vein occlusion. *Am J Ophthalmol*. 2022; 240:330-341.
2. MacCormick JC, Maude RJ, Beare NAV, et al. Grading fluorescein angiograms in malarial retinopathy. *Malar J*. 2015; 14:367.
3. Corkery E, Domalpally A, Blodi B. Image quality assessment of ultra-wide field fluorescein angiogram (UWF-FA) images. *Invest Ophthalmol Vis Sci*. 2020; 61(7):5307.

Sickle Cell Retinopathy: Past Lessons, Future Directions

Adrienne W Scott MD

Introduction

Sickle cell disease (SCD) is the most common inherited blood disorder, affecting millions worldwide. Abnormal hemoglobin polymerizes within erythrocytes, resulting in episodic vaso-occlusion and ongoing vascular endothelial cell damage. Sickle cell retinopathy results from progressive tissue ischemia and a stepwise progression of vascular remodeling that can result in pathologic neovascularization.[1]

Background Observations

Proliferative sickle cell retinopathy (PSR) is the most common cause of vision loss impairment and blindness in SCD, most commonly due to vitreous hemorrhage and retinal detachment from peripheral retinopathy, and it typically progresses between ages 20 and 30.[2] The gold-standard treatment for PSR remains scatter laser photocoagulation, which decreases incidence of vitreous hemorrhage compared to observation.[3] Anti-VEGF has shown utility as an off-label adjunctive treatment for PSR.[4]

Though known primarily as a proliferative retinopathy, macular involvement in SCD is also common. Macular vaso-occlusion and thinning have been demonstrated on OCT and OCT angiography (OCT-A) in SCD patients as young as 5 years old.[5] Macular thinning in SCD is progressive with age, and hydroxyurea use may be protective against macular thinning.[6] Multimodal imaging including OCT, OCT-A, ultrawide-field fundus photography (UWF-FP), and ultrawide-field fluorescein angiography are useful to evaluate retinal ischemia.

Future Directions

Current screening guidelines for sickle cell retinopathy, based on expert consensus, recommend SCD patients undergo retinal evaluation every 1-2 years beginning at age 10.[7] Telescreening to detect PSR through nonmydriatic UWF-FP taken in a hematology clinic may improve screening efficiency.[8] Additionally, machine learning algorithms may have potential applications in PSR screening.[9]

Innovations in systemic disease–modifying treatments, including gene therapies and gene editing, bone marrow transplantation, and novel pharmacotherapeutic agents, show promise. Retinal imaging in SCD patients receiving these treatments may provide further insights into the relationship between the systemic circulation and the retinal microvasculature.

References

1. Goldberg MF. Classification and pathogenesis of proliferative sickle retinopathy. *Am J Ophthalmol*. 1971; 71(3):649-665.
2. Goldberg MF. Natural history of untreated proliferative sickle retinopathy. *Arch Ophthalmol*. 1971; 85(4):428-437.
3. Farber MD, Jampol LM, Fox P, et al. A randomized clinical trial of scatter photocoagulation of proliferative sickle cell retinopathy. *Arch Ophthalmol*. 1991; 109(3):363-367.
4. Cai CX, Linz MO, Scott AW. Intravitreal bevacizumab for proliferative sickle retinopathy: a case series. *J Vitreoret Dis*. 2018; 2:32-38.
5. Ong SS, Linz MO, Li X, Liu TYA, Han IC, Scott AW. Retinal thickness and microvascular changes in children with sickle cell disease evaluated by optical coherence tomography (OCT) and OCT angiography. *Am J Ophthalmol*. 2020; 209:88-98.
6. Lim JI, Niec M, Sun J, Cao D. Longitudinal assessment of retinal thinning in adults with and without sickle cell retinopathy using spectral-domain optical coherence tomography. *JAMA Ophthalmol*. 2021; 139(3):330-337.
7. Yawn BP, Buchanan GR, Afenyi-Annan AN, et al. Management of sickle cell disease: summary of the 2014 evidence-based report by expert panel members. *JAMA* 2014; 312(10):1033-1048. Erratum in: *JAMA* 2014; 312(18):1932 and *JAMA* 2015; 313(7):729.
8. Ahmed I, Pradeep T, Goldberg MF, et al. Nonmydriatic ultra-widefield fundus photography in a hematology clinic shows utility for screening of sickle cell retinopathy. *Am J Ophthalmol*. 2022; 236:241-248.
9. Cai S, Parker F, Urias MG, Goldberg MF, Hager GD, Scott AW. Deep learning detection of sea fan neovascularization from ultra-widefield color fundus photographs of patients with sickle cell hemoglobinopathy. *JAMA Ophthalmol*. 2021; 139(2):206-213.

Intervortex Vein Anastomoses in High Myopia and Their Associations With Chorioretinal Diseases

Kyoko Ohno-Matsui MD and Hongshuang Lu MD

Introduction

The choroid is made up of abundant blood vessels, and the choroidal veins are usually drained into 4 to 8 vortex veins (VVs) located in 4 functional quadrants with clear horizontal and vertical watershed zones.[1] Earlier studies have shown there is an asymmetrical distributions of the VVs even in normal eyes.[2] Also reported was the presence of inter-VV anastomosis in eyes with retinochoroidal diseases[3-5] and in eyes with pachychoroid spectrum diseases.[6-8] The importance of the anastomoses on the development of the pachyvessels and macular pathologies was discussed by these authors. These findings suggested that the underlying status of the choroidal venous outflow may be related to the development of various complications in the posterior fundus.

Inter-VV anastomoses have been detected in various pathological conditions such as carotid cavernous fistula, VV occlusion after scleral buckling surgery,[3] and recently in pachychoroid spectrum diseases.[6] Summarizing all of the data, Spaide et al[9] proposed a new type of disease entity called "venous overload choroidopathy."

A lot of attention has been paid to the importance of inter-VV anastomoses, especially in pachychoroid spectrum diseases such as central serous chorioretinopathy (CSC). Among the many interrelated factors associated with the development of VV anastomoses, one of the main factors is believed to be a thick sclera. Thus, Imanaga et al[10] reported that the anterior sclera was thicker in eyes with CSC than in those without CSC. Using B-scan ultrasonography, Spaide et al[11] recently reported that both the subfoveal and the equatorial sclera were significantly thicker in eyes with CSC than in control eyes. It is expected that the scleral passageway of the exiting VV is lengthened in proportion with the increased scleral thickness.

Various Changes of Choroid and Sclera in Highly Myopic (HM) Eyes

It is known that the sclera and choroid are very thin in HM eyes, and in keeping with this, CSC tends not to develop in HM eyes. In addition, a posterior staphyloma can develop in eyes with severe myopia, and the eye is said to have "pathologic myopia."

It is also known that the large choroidal veins can undergo various alterations, such as a change in the diameter, the formation of macular vortex veins, and a selective disappearance of the larger choroidal veins.[12] These alterations are more obvious in eyes with a staphyloma, although they were also seen in HM eyes without a staphyloma or chorioretinal atrophic changes.

In our myopia center, we have examined many cases with inter-VV anastomoses in HM eyes. We expected that the findings in these eyes may provide new perspectives on the pathogenesis of inter-VV anastomoses.

Various Patterns of Inter-VV Anastomoses in HM Eyes

In a recent study from our department, inter-VV anastomoses were found in 25 of 175 HM eyes (14.29%). In some eyes, the anastomosis was observed near the watershed zone of different VVs (see Figure 1). In such cases, the hallmark changes were the highly tortuous and dilated terminal vessels as seen in eyes with CSC.

In other HM eyes, a more "mature" appearing anastomosis without obvious venous tortuosity was seen (see Figure 2). Such anastomoses occurred through large trunks even in eyes without a posterior staphyloma and with tessellated fundus alone (Figure 2).

In more severely myopic eyes, one or only a few large trunks connecting different VVs were seen (see Figure 3). Interestingly, in the eyes with more mature anastomosis through large trunks, the tortuosity of the anastomotic vessels was no longer obvious.

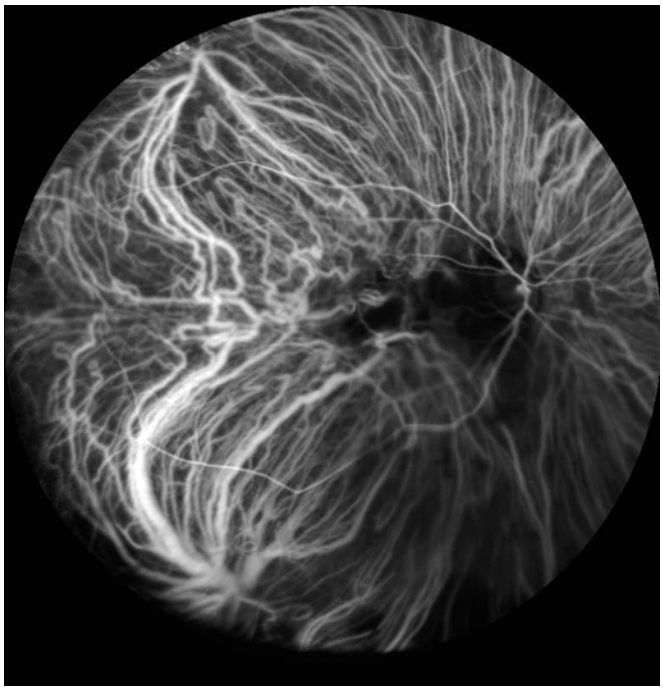


Figure 1. Inter–vortex vein (VV) anastomoses between upper and lower VVs in a highly myopic eye with axial length of 27.2 mm.

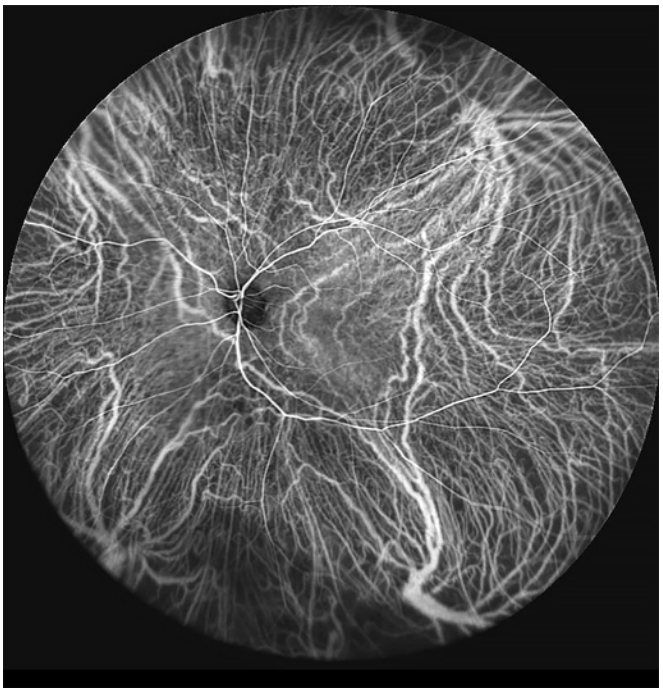


Figure 2. Direct communication between upper and lower vortex vein in a highly myopic eye with axial length of 26.0 mm without a staphyloma.

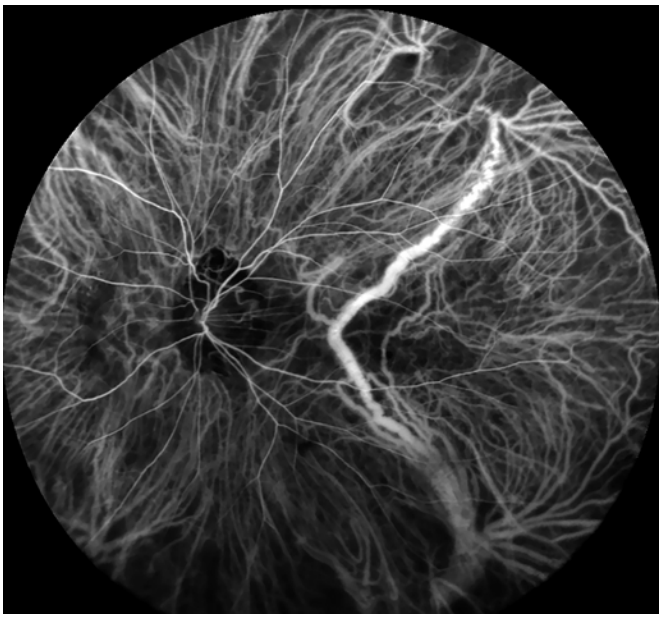


Figure 3. Direct communication through a large trunk between upper and lower vortex vein in a highly myopic eye with axial length of 29.8 mm with a staphyloma.

Is the inter-VV anastomosis in HM eyes an unstable and transient phenomenon?

It would be interesting to know in which direction the choroidal venous blood flows when the upper and lower VV are directly connected through a large channel. Indocyanine green angiography (ICG-A) videos in our cases showed that the blood flow within a large anastomotic channel consisted of flow in 2 different directions. The choroidal venous blood that flowed toward the lower VV was filled first in a pulsatile fashion in the left half of the trunk, and then the right half, which connected to the superior and inferior VVs, was gradually filled. Cheung and colleagues[13] reported pulsatile blood flow in pachyvessels in the watershed zones in eyes with pachychoroid diseases. It was suggested that the blood flow within anastomotic channels is unstable and probably undergoes constant remodeling. In this OCT-A era, ICG-A and especially ICG-A video can provide important information on the blood flow.

A long-term study of HM eyes with inter-VV anastomoses through a large trunk showed that the anastomotic vessels regressed and narrowed during the follow-up period (see Figure 4). Because the venous flow within a large trunk is unstable and sometimes flows in a different direction within that trunk, choroidal venous structures might change to seek lower resistance routes.

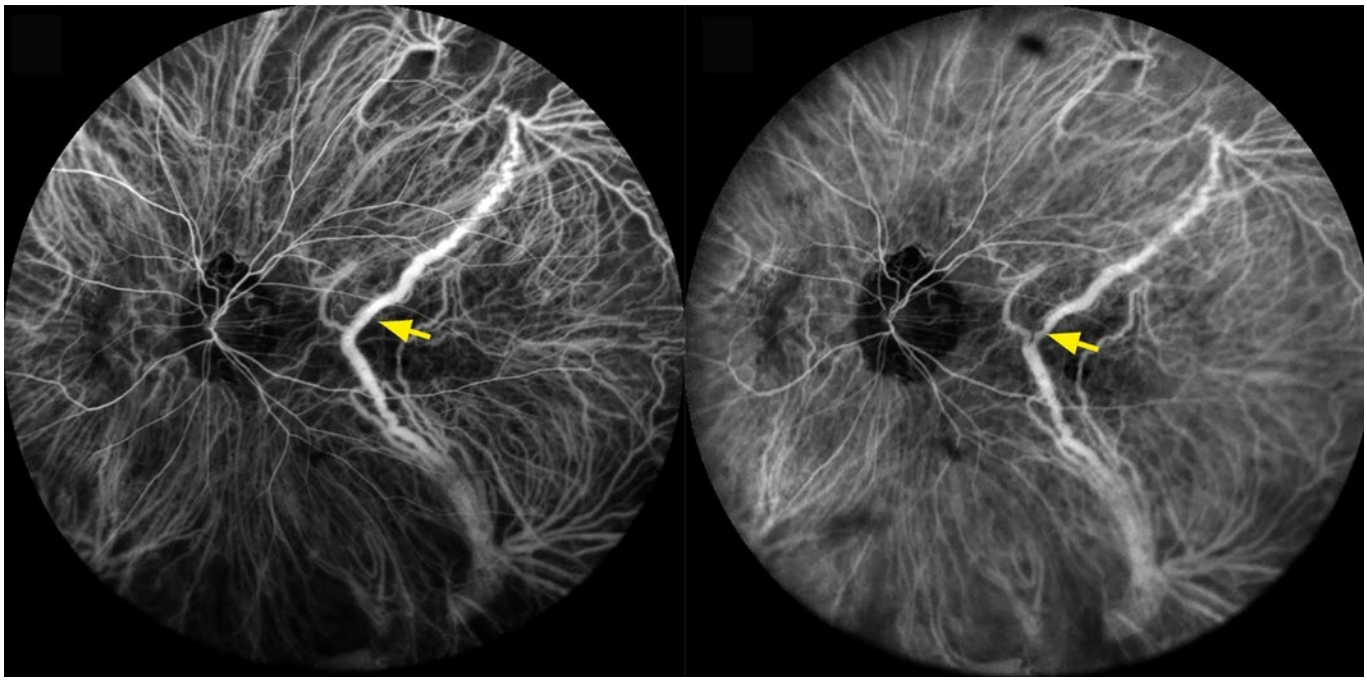


Figure 4. Narrowing of the anastomotic trunk near the fovea (arrow) between the years 2018 (left) and 2021 (right).

Why do inter-VV anastomoses occur in HM eyes with thin sclera?

Our study showed that inter-VV anastomoses also occurred in HM eyes with thin sclera and thin choroid. Many researchers may think that the posterior staphyloma would act as a scleral buckle, and the staphyloma would cause the inter-VV anastomosis by blocking the venous flow toward the peripheral VV. The inter-VV anastomoses appeared to be more "mature" in HM eyes with a staphyloma. In these eyes, the tortuosity of anastomotic vessels was no longer obvious. However, our findings showed that inter-VV anastomoses were still present even in HM eyes without a staphyloma or with a tessellated fundus alone (Figure 2). The pathogenesis of inter-VV anastomoses in HM eyes is difficult to determine. The simple fact of an increased distance from the posterior pole to peripheral VV or a change in the course of the intrascleral part of the VV may be possibilities. However, further studies are needed.

Determining the pathogenesis of inter-VV in various diseases may give us some important clues in understanding this unusual hemodynamic finding. Finally, even in this OCT-A era it should be remembered that ICG-A, including ICG-A videos, is important when examining eyes with VV anastomoses.

References

1. Hayreh S. Segmental nature of the choroidal vasculature. *Br J Ophthalmol*. 1975; 59:631-648.
2. Mori K, Gehlbach PL, Yoneya S, Shimizu K. Asymmetry of choroidal venous vascular patterns in the human eye. *Ophthalmology* 2004; 111:507-512.
3. 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.
4. Sutoh N, Muraoka K, Takahashi K, Ikeda F, Shimizu K. Remodelling of choroidal circulation in carotid cavernous sinus fistula. *Retina* 1996; 16:497-504.
5. Takahashi K, Kishi S, Muraoka K, Tanaka T, Shimizu K. Radiation choroidopathy with remodeling of the choroidal venous system. *Am J Ophthalmol*. 1998; 125:367-373.
6. Matsumoto H, Hoshino J, Mukai R, et al. Vortex vein anastomosis at the watershed in pachychoroid spectrum diseases. *Ophthalmol Retina*. 2020; 4:938-945.
7. Matsumoto H, Kishi S, Mukai R, Akiyama H. Remodeling of macular vortex veins in pachychoroid neovasculopathy. *Sci Rep*. 2019; 9(1):14689.
8. Spaide RF, Ledesma-Gil G, Gemmy Cheung CM. Intervortex venous anastomosis in pachychoroid-related disorders. *Retina* 2021; 41:997-1004.
9. 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*. 2021; 100973.
10. Imanaga N, Terao N, Nakamine S, et al. Scleral thickness in central serous chorioretinopathy. *Ophthalmol Retina*. 2021;5:285-291.
11. Spaide RF, Fisher YL, Ngo WK, Barbazetto I. Regional scleral thickness as a risk factor for central serous chorioretinopathy. *Retina* 2022; 42(7):1231-1237.
12. Moriyama M, Ohno-Matsui K, Futagami S, et al. Morphology and long-term changes of choroidal vascular structure in highly myopic eyes with and without posterior staphyloma. *Ophthalmology* 2007; 114:1755-1762.
13. Cheung GCM, Teo KYC, Spaide RF. Pulsatile filling of pachyvessels in watershed zones in pachychoroid disease. *Retina*. In press.

Choroidal Disturbance in Polypoidal Choroidal Vasculopathy: Insights From Dynamic Indocyanine Green Angiography

Gemmy Chui Ming Cheung MB BChir FRCOphth

Dilated choroidal veins and inter-vortex anastomosis are frequently seen in eyes with central serous chorioretinopathy and polypoidal choroidal vasculopathy. Recent research suggests that these features may result from chronic venous remodeling in response to venous outflow obstruction. By studying dynamic indocyanine green angiography, several different patterns of alterations in choroidal filling can be seen, including prolonged arterio-venous transit, pulsatile flow, and retrograde flow. These findings suggest there may be several types of mechanical disturbance that contribute to the venous remodeling observed.

N-of-1 Clinical Trials: A Scientific Approach to Personalized Medicine for Patients With Rare Retinal Diseases Such as Retinitis Pigmentosa

Marco A Zarbin MD PhD FACS and Gary Novack PhD

I. Retinitis Pigmentosa (RP)
   A. A group of inherited retinal degenerative diseases with a prevalence of approximately 1 in 4000, affecting 2 million persons globally
   B. Genetically heterogeneous: associated with more than 3000 mutations in approximately 100 genes
   C. >50 ongoing retinal gene therapy clinical trials, most for relatively rare diseases such as RP

II. Two Problems Confronting RP Clinical Trials
   A. Small target patient population
   B. Patient heterogeneity

III. What are N-of-1 trials?
   A. Randomized, prospective, controlled, multiple crossover trials in a single patient (see Figure 1)
   B. Effects of 1 or more treatments are studied by following individual patients:
      1. Patients receive alternative treatments (eg, therapeutic intervention, placebo, standard of care) for prespecified time intervals ("periods").
      2. Various treatments alternate in a randomized order through several ($n \geq 3$) crossover periods ("blocks").
      3. May include a "run-in" period, which might assess patient tolerance and adherence as well as permit washout of previous treatments
      4. Depending on pharmacokinetics of proposed intervention, washout periods might be interposed between different treatment assignments or could serve as placebo treatment periods.
   C. Ideally, patients, physicians, and data analysts are masked.
   D. Can have randomized allocation to treatment cycles if cycles differ in structure

IV. Some Features of N-of-1 Trials
   A. Aggregated N-of-1 trials constitute Level I evidence (as do systematic reviews of randomized trials).[2] Parallel group randomized clinical trials (RCTs) provide Level II evidence.
   B. N-of-1 trial design
      1. A subgroup of RCTs
      2. Resembles a crossover RCT, but is just for 1 person at a time
   C. Experimental protocols of parallel group RCTs can be used, eg, allocation concealment and double-masking.
   D. N-of-1 trials allow one to assess efficacy in an individual subject (since each subject participates in the treatment and control group at different times).
   E. Each subject's data comprise the result of a randomized trial provided the trial design is appropriate.
   F. Parallel group RCTs cannot assess treatment benefit in an individual patient since subjects are enrolled either in the treatment or control group but not both.
   G. The aggregated data (treatment vs. control) of a parallel group RCT comprise the result of 1 trial only.

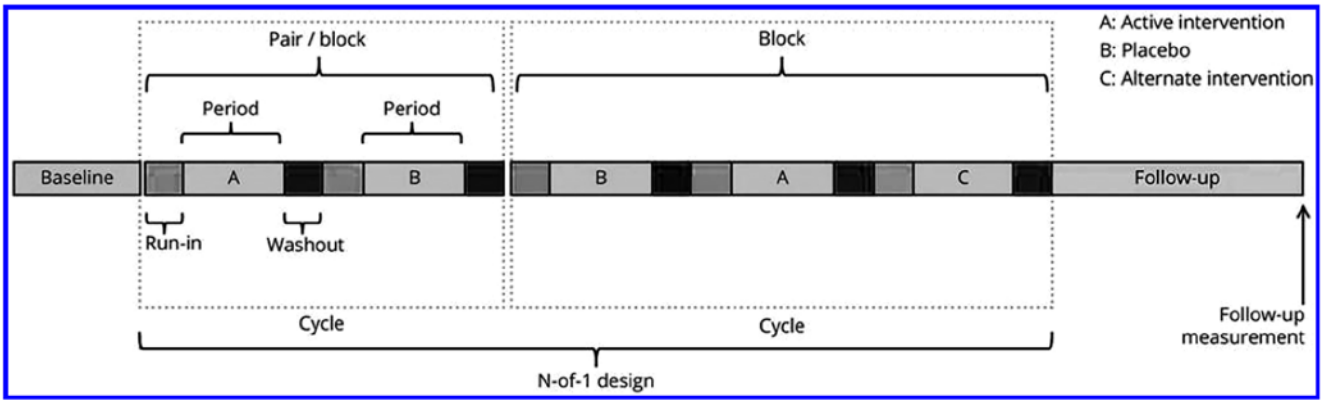


Figure 1. Example of N-of-1 trial design and terminology. Source: Muller AR, Brands M, van de Ven PM, et al. Systematic review of N-of-1 studies in rare genetic neurodevelopmental disorders: the power of 1. *Neurology* 2021; 96(11):529-540.

V. Four Advantages of N-of-1 Trials

A. Each patient is assured exposure to the experimental treatment, which may facilitate recruitment. This trial design also might be attractive to the parents of children with RP.

B. Each patient serves as his/her own control, which reduces variance (compared to between-patient variability) and minimizes confounding.

C. There is substantial patient input on efficacy and safety, which may simplify clinical decision making if the aggregated data do not demonstrate a treatment effect for the overall population.

1. Since each N-of-1 trial is a crossover RCT involving 1 subject, if the trial result in this particular subject clearly demonstrates a treatment benefit, then it may be appropriate to recommend the therapy despite the null result of the aggregated data.

2. Aggregated data are essential: they guide initial clinical recommendations for patients not enrolled in the trial.

D. Enrollment of patients with comorbidities, generally discouraged in parallel group RCTs, is more easily managed in this trial design, since each patient serves as their own control.

E. It may be easier to identify treatment effects, or lack thereof, in specific subpopulations of patients in contrast to parallel group RCTs.

VI. Limitations of N-of-1 Trials

A. N-of-1 trials are appropriate only for specific types of conditions and treatments (see Table 1).

B. Patient dropout in N-of-1 studies has disproportionate impact vs. parallel group RCTs since each participant contributes at least twice the information compared to an equivalent parallel group RCT. (Subjects contribute to both treatment and control arms of the study.)

C. If effect of a treatment period affects subsequent periods (excluding washout periods), then a carryover effect is present.

1. Carryover effects can complicate study design, eg, compromise estimation of treatment effect, resulting in need for large sample size to have adequate statistical power. Persistence of a treatment effect into the subsequent period of a block invalidates measurement of the primary outcome during the second period.

2. Carryover effect can be avoided by including a washout period between treatment periods or by randomizing block duration as well as treatment assignment.

D. If cycles in the N-of-1 trial are long, then a confounder known as the "period effect" may become important. Period effects occur when difference in outcome is attributable to the calendar time in which treatment is received (eg, symptom under treatment is exacerbated in winter and ameliorated in summer).

VII. Some Clinical Scenarios in Which N-of-1 Design Is Considered[3]

VIII. N-of-1 Trial Summary

A. Randomized, prospective, controlled, multiple crossover trials in a single patient

B. Effects of 1 or more treatments are studied by following individual patients who receive alternative treatments (eg, therapeutic intervention, placebo).

C. May provide a path to assess treatments for rare diseases with rigor equal to or greater than that of parallel group randomized clinical trials *if*:

1. Disease is reasonably stable during the trial *and*

2. Disease has a sign/symptom that responds *reversibly* to the therapy *and*

3. Sign/symptom (primary endpoint) can be measured repeatedly.

D. N-of-1 trials may improve feasibility and affordability of clinical trials for patients with rare retinal diseases.

Table 1. Features of Conditions and Therapies That Favor the Use of an N-of-1 Trial Design

Condition	Treatment
Rare (small patient population)	Ameliorates but does not cure the disease
Chronic	Reversible effect on primary outcome
Slowly progressive during the trial	Relatively rapid onset of measured effect after exposure and rapid cessation after withdrawal
Primary outcome is clinically important, repeatedly measurable, and treatable.	Must induce changes that are measurable repeatedly and clinically relevant

Source: Zarbin MA, Novack G. N-of-1 clinical trials: a scientific approach to personalized medicine for patients with rare retinal diseases such as retinitis pigmentosa. *J Ocul Pharmacol Ther.* 2021; 37(9):495-501.

References

1. Muller AR, Brands M, van de Ven PM, et al. Systematic review of N-of-1 studies in rare genetic neurodevelopmental disorders: the power of 1. *Neurology* 2021; 96(11):529-540.
2. Howick J, Chalmers I, Glasziou P, et al. The Oxford 2011 Levels of Evidence. *Oxford Centre for Evidence-Based Medicine*. 2011; https://www.cebm.net/2016/05/ocebm-levels-of-evidence/.
3. Zarbin MA, Novack G. N-of-1 clinical trials: a scientific approach to personalized medicine for patients with rare retinal diseases such as retinitis pigmentosa. *J Ocul Pharmacol Ther.* 2021; 37(9):495-501.

Current Status of "Liquid" Biopsy for Uveal Melanoma

Ivana K Kim MD

I. Blood Biomarkers Assayed in Uveal Melanoma
   A. Circulating tumor cells (CTCs)[1]
      1. A multimarker capture technique can detect CTCs in >90% of cases of primary uveal melanoma.
      2. Inconsistent correlation between CTCs and clinical prognostic features and survival
      3. Genetic analyses of CTCs possible
      4. Capture rate quite variable depending on blood collection methods as well as detection protocol
   B. Circulating tumor DNA (ctDNA)
      1. Commercial tests steadily increasing
         a. Companion diagnostics to determine eligibility for targeted therapy in other solid cancers[2]
         b. Tool for assessment of minimal residual disease[3]
      2. Detection rates of ctDNA in primary uveal melanoma quite variable[1,4,5]
      3. ctDNA is more consistently detected in metastatic uveal melanoma.[1,6] Levels are correlated with tumor volume, survival.
   C. Circulating microRNA (miRNA)[1]
      1. Exploratory phase
      2. Differential expression evaluated
         a. Primary uveal melanoma vs. metastatic melanoma vs. controls[7]
         b. Cases with monosomy 3 vs. those without[8]

II. Clinical Indications for Application of Liquid Biopsy
   A. Response to therapy in metastatic disease
      1. ctDNA reduction correlated better with overall survival than reduction in tumor size in patients treated with tebentafusp. (Shoushtari AN, Collins L, Espinosa E, et al. 2021 ESMO Annual Congress. Abstract 17570.)
      2. ctDNA useful in predicting clinical benefit and detecting disease progression in trial of protein kinase C inhibition[9]
   B. Early detection of disease progression
      1. Possible role in surveillance for metastatic disease[10]
      2. MRI more sensitive than Guardant360 ctDNA assay (Weight RM, Sato S, Orloff MM, Mastrangelo MJ, Sato T. 2016 ASCO Annual Meeting, Abstract 9569.)
   C. Response to adjuvant therapy
   D. Differentiating nevus vs. melanoma?

References

1. Beasley A, Isaacs T, Khattak MA, et al. Clinical application of circulating tumor cells and circulating tumor DNA in uveal melanoma. *JCO Precis Oncol.* 2018; 2:PO.17.00279.
2. Page RD, Drusbosky LM, Dada H, et al. Clinical outcomes for plasma-based comprehensive genomic profiling versus standard-of-care tissue testing in advanced non-small cell lung cancer. *Clin Lung Cancer.* 2022; 23(1):72-81.
3. Loupakis F, Sharma S, Derouazi M, et al. Detection of molecular residual disease using personalized circulating tumor DNA assay in patients with colorectal cancer undergoing resection of metastases. *JCO Precis Oncol.* 2021; 5:PO.21.00101.
4. Bustamante P, Tsering T, Coblentz J, et al. Circulating tumor DNA tracking through driver mutations as a liquid biopsy-based biomarker for uveal melanoma. *J Exp Clin Cancer Res.* 2021; 40(1):196.
5. Beasley A, Isaacs T, Khattak MA, et al. Clinical application of circulating tumor cells and circulating tumor DNA in uveal melanoma. *JCO Precis Oncol.* 2018; 2:PO.17.00279.
6. Bidard FC, Madic J, Mariani P, et al. Detection rate and prognostic value of circulating tumor cells and circulating tumor DNA in metastatic uveal melanoma. *Int J Cancer.* 2014; 134(5):1207-1213.
7. Triozzi PL, Achberger S, Aldrich W, et al. Association of tumor and plasma microRNA expression with tumor monosomy-3 in patients with uveal melanoma. *Clin Epigenetics.* 2016; 8:80.
8. Stark MS, Gray ES, Isaacs T, et al. A panel of circulating microRNAs detects uveal melanoma with high precision. *Transl Vis Sci Technol.* 2019; 8(6):12.
9. Park JJ, Diefenbach RJ, Byrne N, et al. Circulating tumor DNA reflects uveal melanoma responses to protein kinase C inhibition. *Cancers (Basel)* 2021; 13(7):1740.
10. Francis JH, Canestraro J, Brannon AR, et al. Association of plasma circulating tumor DNA with diagnosis of metastatic uveal melanoma. *JAMA Ophthalmol.* 2021; 139(11):1244-1245.

Conditional Survival in Uveal Melanoma: This is what the patient wants to know.

Carol L Shields MD

I. What is the Cancer Genome Atlas (TCGA)?
   A. TCGA project was conceived in 2006 by the National Cancer Institute to study 33 human cancers.
      1. Also called the "Human Cancer Genome Project"
      2. Studied uveal melanoma in 80 cases
      3. Used multiplatform analysis with chromosome copy number alterations, DNA methylation status, RNA expression, protein translation, and immune markers
      4. Discovered a basic 4-group classification for uveal melanoma listed as Groups A, B, C, D
         a. Groups A and B are low risk for metastasis.
         b. Groups C and D are high risk for metastasis.

II. What are the types of survival?
   A. Nonconditional survival = static
      1. Estimated from date first seen
      2. Usually to 5- and 10-year outcomes
      3. Most commonly used form of survival
   B. Conditional survival = dynamic
      1. Estimated from multiple dates
      2. For example,
         a. "If I live for 2 years what is my survival at 5 years?"
         b. "If I live for 5 years what is my survival at 10 years?"

III. What has been published regarding uveal melanoma survival?
   A. Two reports
      1. Zabor et al. Conditional survival in uveal melanoma. *Ophthalmol Ret*. 2021: Evaluated overall survival in SEER database at several intervals up to 10 years (see Figure 1).
      2. Shields et al. Conditional survival of uveal melanoma using the Cancer Genome Atlas Classification in 1001 cases. *Saudi J Ophthalmol*. In press (see Figure 2).

      Figure 3 shows the outcomes based on nonconditional and conditional survival for Groups A, B, C, and D at 10 years.
   B. The longer a patient survives without metastasis, the less likely they are to develop metastasis per TCGA.

Figure 1

Conditional Survival in Uveal Melanoma

Emily C. Zabor, DrPH,[1] Tomas Radivoyevitch, PhD,[1] Arun D. Singh, MD,[2] Emine Kilic, MD, PhD,[3] J.E.M.M. de Klein, PhD,[4] Helen Kalirai, PhD,[5] Sarah E. Coupland, PhD[5]

Purpose: To investigate conditional survival in patients with uveal melanoma in the United States.
Design: Cohort study.
Participants: Patients were identified using International Classification of Disease for Oncology, Third Edition, codes for both morphologic features (melanoma, 8720–8790) and site (retina, C69.2; choroid, C69.3; and ciliary body, C69.4) from 1975 through 2011 using the Surveillance, Epidemiology, and End Results (SEER) database SEER 18.
Methods: Observed metastasis-free survival (MFS) and overall survival (OS) were estimated using the Kaplan-Meier method. Conditional metastasis-free survival (cMFS) and conditional overall survival were calculated based on the observed MFS and OS. Relative survival also was calculated using the actuarial method. Survival to 5 and 10 years after diagnosis were calculated, conditioned on various numbers of years already survived.
Main Outcome Measures: Conditional MFS, conditional OS, and conditional relative survival.
Results: A total of 6863 cases of uveal melanoma were identified. Median follow-up among survivors was 11 years. During follow-up, 3883 patients died of any cause, and of these, 2131 deaths were the result of metastatic uveal melanoma. The nonconditional 5-year MFS was 80%. After surviving 1, 2, 3, or 4 years after diagnosis, the 5-year cMFS estimates increased to 82%, 87%, 92%, and 96%, respectively. The nonconditional MFS at 10 years was estimated to be 69%. After having survived 5, 6, 7, 8, or 9 years after diagnosis, the 10-year cMFS estimates increased to 87%, 90%, 93%, 96%, and 98%, respectively. This result pattern was confirmed with estimates of relative survival.
Conclusions: Conditional survival estimates of uveal melanoma improve with time since primary diagnosis. Among patients who already have survived for at least 5 years, 10-year conditional survival rates are high. Conditional survival analysis can provide specific guidance for counselling patients. *Ophthalmology Retina 2021;5:536-542 © 2020 by the American Academy of Ophthalmology*

Figure 2

Conditional survival of uveal melanoma using the cancer genome atlas classification in 1001 cases

Carol L. Shields, Philip W. Dockery, Eileen L. Mayro, Zeynep Bas, Antonio Yaghy, Sara E. Lally, Marlana Orloff[1], Takami Sato[1], Jerry A. Shields

Access this article online
Quick Response Code:
Website: www.saudijophthalmol.org
DOI: 10.4103/SJOPT.SJOPT_69_21

Abstract:

OBJECTIVE: To understand conditional prognostic value of the Cancer Genome Atlas (TCGA) for uveal melanoma metastasis based on event-free survival at 1, 2, 3, 4, and 5 years.

METHODS: A retrospective study of eyes with uveal melanoma categorized according to TCGA and studied for nonconditional and conditional risks for metastasis at 5 and 10 years.

RESULTS: Of 1001 eyes with uveal melanoma, the nonconditional (standard, at presentation) 5-year/10-year metastatic rate was 18%/25%. The conditional 5-year/10-year metastatic rate (for those without metastasis at 2 years) revealed 10%/18% and the conditional 10-year metastatic rate (for those without metastasis at 5 years) revealed 9%. The TCGA categories included Group A (n = 486, 49%), B (n = 141, 14%), C (n = 260, 26%), and D (n = 114, 11%). The non-conditional 5-year/10-year metastatic rate revealed Group A (4%/6%), Group B (12%/20%), Group C (23%/49%), and Group D (60%/68%). The conditional 5-year/10-year metastatic rate (for those without metastasis at 2 years) revealed Group A (2%/5%), Group B (8%/18%), Group C (21%/40%), and Group D (38%/50%). The conditional 10-year metastatic rate (for those without metastasis at 5 years) revealed Group A (2%), Group B (10%), Group C (33%), and Group D (20%). The peak incidence of metastasis for Groups A and B occurred during years 5–6, C during years 4–6, and D during years 1–2.

CONCLUSION: Survival outcomes for uveal melanoma as non-conditional (at presentation) and conditional (event-free survival during follow-up) reveal reduction in metastatic rate over time. For those with 5-year metastasis-free survival, the 10-year conditional risk for metastasis was 9%.

Keywords:

Choroid, conditional, genetics, melanoma, survival, The Cancer Genome Atlas, Uvea

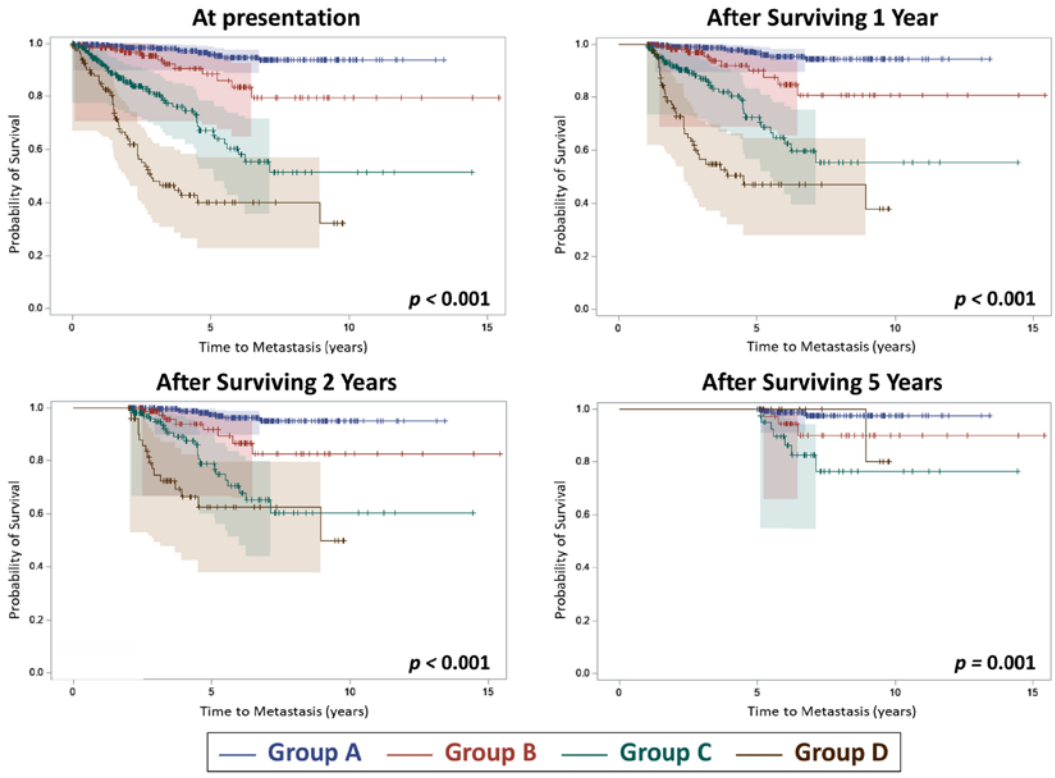


Figure 3. Upper left: Non-conditional survival from date first seen at 10 years. Upper right: Conditional survival at 10 years, after surviving 1 year. Bottom left: Conditional survival at 10 years, after surviving 2 years. Bottom right: Conditional survival at 10 years, after surviving 5 years.

Contemporary Precision Diagnosis and Management of Vitreoretinal Lymphoma

J William Harbour MD

Primary Vitreoretinal Lymphoma (PVRL)

- Variant of primary CNS lymphoma
- Usually large, B-cell, non-Hodgkin lymphoma
- Bilateral in >80%
- Typically diagnosed in fifth to seventh decades
- ~90% develop CNS lymphoma.
- ~10% with CNS lymphoma develop PVRL.

Clinical Features

- Vitreous cell
- Sub–retinal pigment epithelial (RPE), subretinal, retinal infiltrates

Systemic Workup

- Brain MRI
- Lumbar puncture for CSF analysis

Biopsy Techniques

- Vitreous biopsy
- Subretinal/sub-RPE aspiration
- Retinal and retinochoroidal biopsy

Diagnostic Testing

- Cytology and immunocytochemistry
- Flow cytometry
- Polymerase chain reaction for immunoglobulin heavy chain rearrangement
- Intraocular IL-6/IL-10 ratio
- MYD88 mutation

Treatment Options

- External beam radiotherapy
- Systemic chemotherapy
- Intravitreal chemotherapy
- Intrathecal chemotherapy

Selected Readings

1. Berenbom A, Davila RM, Lin HS, Harbour JW. Treatment outcomes for primary intraocular lymphoma: implications for external beam radiotherapy. *Eye* 2007; 21:1198-1201.
2. Bonzheim I, Giese S, Deuter C, et al. High frequency of MYD88 mutations in vitreoretinal B-cell lymphoma: a valuable tool to improve diagnostic yield of vitreous aspirates. *Blood* 2015; 10.1182/blood-2015-01-620518.
3. Chan CC, Rubenstein JL, Coupland SE, et al. Primary vitreoretinal lymphoma: a report from an International Primary Central Nervous System Lymphoma Collaborative Group symposium. *Oncologist* 2011; 16:1589-1599.
4. de la Fuente MI, Alderuccio JP, Reis IM, et al. Bilateral radiation therapy followed by methotrexate-based chemotherapy for primary vitreoretinal lymphoma. *Am J Hematol*. 2019; 94:455-460.
5. Farkas T, Harbour JW, Davila RM. Cytologic diagnosis of intraocular lymphoma in vitreous aspirates. *Acta Cytol*. 2004; 48:487-491.
6. Hiemcke-Jiwa LS, Ten Dam-van Loon NH, Leguit RJ, et al. Potential diagnosis of vitreoretinal lymphoma by detection of MYD88 mutation in aqueous humor with ultrasensitive droplet digital polymerase chain reaction. *JAMA Ophthalmol*. 2018; 136(10):1098-1104.
7. Larkin KL, Saboo US, Comer GM, et al. Use of intravitreal rituximab for treatment of vitreoretinal lymphoma. *Br J Ophthalmol*. 2014; 98:99-103.
8. Rajagopal R, Harbour JW. Diagnostic testing and treatment choices in primary vitreoretinal lymphoma. *Retina* 2011; 31:435-440.
9. Riemens A, Bromberg J, Touitou V, et al. Treatment strategies in primary vitreoretinal lymphoma: a 17-center European collaborative study. *JAMA Ophthalmol*. 2015; 133:191-197.

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: Biologics
   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

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 diftitox	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 HER-2 protein	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

(table continues on next page)

Class	Drugs	Mechanism	Retinal Side Effects
Small Molecule Inhibitors (continued)			
	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 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 CTLA-4	Panuveitis Uveitis Vitritis Optic nerve edema Serous retinal detachment Choroidopathy CNV VKH-like syndrome
	Pembrolizumab Nivolumab Cemiplimab Dostarlimab	PD-1 inhibitor	Panuveitis Uveitis Vitritis Optic nerve edema Vasculitis Cystoid macula edema Hypotony Uveal effusion syndrome Immune retinopathy VKH-like syndrome
	Atezolizumab Avelumab Durvalumab	PD-L1 inhibitor	Panuveitis Uveitis Vitritis Optic nerve edema Vasculitis Acute macula neuroretinopathy Uveal effusion syndrome

Abbreviations: HER-2, human epidermal growth factor receptor 2; ALK, anaplastic lymphoma kinase; CTLA-4, cytotoxic T-lymphocyte antigen-4; PD-1, programmed death protein 1; VKH, Vogt-Koyanagi-Harada.

Oncology Panel Discussion

Panel Moderator: Prithvi Mruthyunjaya MD

Panelists: Michael M Altaweel MD, Jesse L Berry MD, Hakan Demirci MD, and Amy C Schefler MD

NOTES

Home OCT Is Going to Be a Boon for Retinal Specialists

Anat Loewenstein MD

The Unmet Need

Anti-VEGF therapies have given clinicians an invaluable tool for addressing wet AMD, the leading cause of blindness in the United States. These therapies have shown promising results in the clinical trials; however, that efficacy hasn't been replicated in the real-world setting.[1]

The driving factor for this has been the burden on physicians, patients, and caregivers of the high-frequency visits and treatments, required by and based on existing protocols. The current methods don't allow for personalization in treatment for this heterogeneous disease.

The role of home OCT becomes even more critical with the approval of several long-acting therapies.

Role of Remote Monitoring

We have learned over the last 2 years that not all clinical activity needs to be performed in the clinician's office. It is critical for our patients that ophthalmologists adopt an optimal approach to remote patient monitoring.

Wet AMD, a chronic disease with rapid onset and changes, is an ideal candidate for remote monitoring. OCT has been the diagnostic partner of anti-VEGF therapies since their adoption 2 decades ago. OCT data obtained at a high frequency would be a natural way to remotely manage such patients. It can provide several critical pieces of information.

Firstly, it can provide deeper understanding of patient response to a chosen drug. Our current standard of care provides sporadic data about the fluid status based on visit timing. More granular temporal information can allow for better decisions around choice of drugs and other treatment parameters. Availability of OCT data at a high temporal frequency would allow for personalization of treatment plans.

Secondly, the presence of remote monitoring will further enhance physician confidence in the use of longer-acting therapies without concern for the patient population that may have more frequent onsets.

Confidence Based on Current State of Home OCT

OCT has been a mainstay for diagnosis and monitoring of wet AMD. Hence, it is a reasonable argument that more granular availability of OCT data can only be a net positive. However, the practicality of such a solution depends heavily on its real-world performance. The promising results published in early studies using home OCT in a fashion very similar to its proposed clinical use help allay these concerns.

In the study carried out by Dr. Jeff Heier and Dr. Nancy Holekamp,[2] patients performed 2380 tests at their home with a 95% success rate. In over 93% of cases, the data obtained provided information about the presence of fluid equivalent to that of in-office OCT. It should be noted that these patients did not receive any prior training at the clinic in the use of self-operated home OCT. In addition, patients reported a highly positive experience over the 90-day use of home OCT. Patients responded positively 97% of the time in relation to convenience of daily imaging and ease of use of the device.

These excellent results related to fidelity of the data obtained by home OCT, the ability of patients to consistently use the self-imaging device, and the degree of patient satisfaction and compliance show the practicality of this remote monitoring technique.

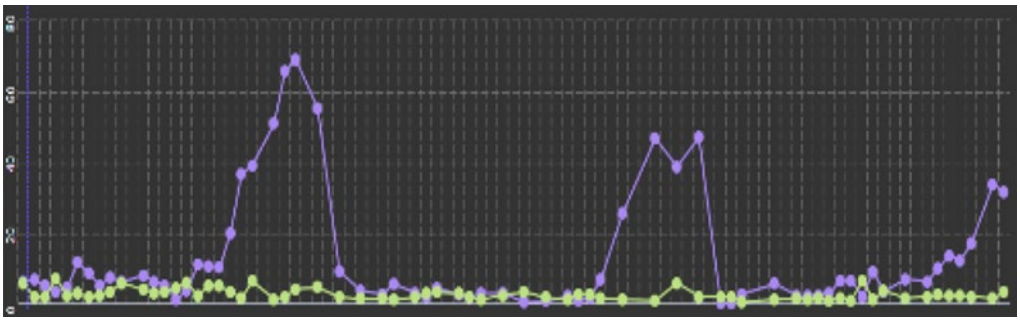
Home OCT: A Remote Monitoring Paradigm and Not Just a Device

The excellent results obtained by use of home OCT are a result of a multifaceted approach, developed through the convergence of multiple technologies and processes over the years. The home OCT device used in the above-mentioned study was supported by modern deep learning–based artificial intelligence (AI) algorithms. The amount of data produced by the daily imaging is indeed difficult for physicians to review and interpret. However, the AI-based fluid detection algorithms allow the conversion of 40 megabytes of daily OCT images into a single parameter, plotted against time. This allows seamless review and interpretation of data by clinicians.

The home OCT goal of reducing physician burden would be negated if the process of introducing the device to the patient were time consuming. The device used in the above-mentioned study was supported by a remote monitoring center that offered patient education services and support via clinically trained staff members. This combination of AI-based data curation and dedicated support in patient management allows for the successful implementation of home OCT.

Ancillary Advantages of Home OCT

Home OCT will certainly improve care for current wet AMD patients. In addition it will play a critical role in improving our overall understanding of the disease and its management. We currently have limited understanding of disease progression and long-term impact of different treatment regimes. Home OCT will provide high-resolution temporal information that adds to a better understanding of disease dynamics across the patient population, potentially creating avenues for development of new disease classifications, therapies, and management paradigms.



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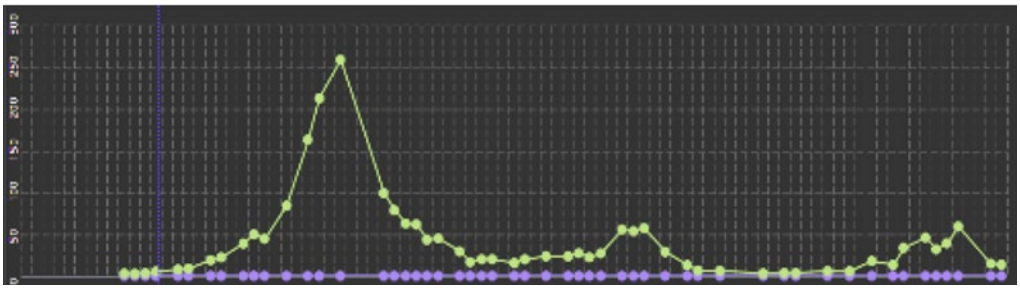

B

Figure 1. Frequent home OCT measurements of intra- (purple) and subretinal (green) fluid volume give actionable insights in disease reactivation and treatment response over a 3-month period.

Conclusion

Ophthalmology faces the serious challenge of a growing number of elderly and a limited number of current and future trained physicians. We need to adopt modern technologies to best serve our patients. Home OCT is a prime example of a virtual extension of physician capability without increasing demands on physician time. Adoption of this technology would be of great benefit for patients, caregivers, and physicians.

References

1. Ho AC, Heier JS, Holekamp NM, et al. Real-world performance of a self-operated home monitoring system for early detection of neovascular age-related macular degeneration. *J Clin Med*. 2021; 10(7):1355.
2. Liu YL, Holekamp NM, Heier JS. Prospective, longitudinal study: daily self-imaging with home OCT for neovascular age-related macular degeneration. *Ophthalmol Retina*. Epub ahead of print 2022 Feb 28. doi: 10.1016/j.oret.2022.02.011.

Home OCT Is Going to Be the Bane of Retina Specialists

Carl C Awh MD

bane [bān]

A source of persistent annoyance or exasperation.

Home OCT may one day allow patients to perform OCT scans at home, with central aggregation of massive amounts of data and with artificial intelligence analysis of the data. Clinical trial data are promising, and the technology is compelling.

However, in this friendly debate, I will present reasons that Home OCT may create significant logistical, clinical, financial, and medicolegal challenges for retina specialists. Home OCT may indeed become a boon to patients but not necessarily to retina specialists! In the near future, home OCT may well be the bane of retina specialists.

Monthly Intravitreal Therapy Is a Feasible Approach for Patients With Geographic Atrophy

Robert B Bhisitkul MD

NOTES

Monthly Intravitreal Therapy Is Impractical for Patients With Geographic Atrophy

Daniel F Martin MD

NOTES

The Port Delivery System Will Be My Preferred Treatment for Neovascular AMD Patients Requiring Frequent Therapy

Caroline R Baumal MD

The Port Delivery System (PDS) is a novel drug delivery device that was recently FDA approved to treat exudative neovascular AMD. This was based on the Phase 3 Archway trial that met its primary endpoint and demonstrated that vision outcomes with the PDS were both noninferior and equivalent to monthly intravitreal ranibizumab injections for neovascular AMD. Ninety-five percent of eyes did not require supplemental anti-VEGF treatment before the study specified office-based refill-exchange procedure every 6 months.

After transscleral surgical implantation, the PDS delivers continuous release of a customized formulation of ranibizumab into the vitreous cavity. This eliminates the need for chronic, frequent, burdensome, and painful intravitreal injections while maintaining the beneficial effects of sustained-release anti-VEGF therapy. Over 90% of PDS patients who had previously received intravitreal injections preferred PDS over IVT injections. Ocular adverse events of special interest for this new device and procedure have been identified, and these can be mitigated with careful patient selection and meticulous surgical technique.

Selected Readings

1. Holekamp NM, Campochiaro PA, Chang MA; Archway Investigators. Archway randomized Phase 3 trial of the port delivery system with ranibizumab for neovascular age-related macular degeneration. *Ophthalmology* 2022; 129(3):295-307.
2. Khanani AM, Callanan D, Dreyer R; Ladder Investigators. 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*. 2021; 5(8):775-787.

Longer-Acting VEGF Agents Will Be My Preferred Treatment for Neovascular AMD Patients Requiring Frequent Therapy

Dante Pieramici MD

NOTES

Surgical Peeling of Epiretinal Membrane Is Appropriate for Patients With Vision 20/25 or Better

Richard S Kaiser MD

NOTES

Surgical Peeling of Epiretinal Membrane Should Be Reserved for Patients With Vision Worse Than 20/40

Judy E Kim MD

Idiopathic epiretinal membrane (ERM) is the most common presentation, while secondary ERMs occur in association with diabetic retinopathy, retinal vein occlusion, ocular inflammatory disease, trauma, intraocular surgery, intraocular tumors, and retinal tear or detachment. Other risk factors include age, posterior vitreous detachment, and history of ERM in the fellow eye.

While the pathophysiology of ERM formation is not completely understood, it is believed that migration of glial cells through defects in the internal limiting membrane (ILM) and into the vitreous cavity causes ERM to develop on the surface of the ILM. This proliferative process is mainly triggered by growth factors and cytokines.

When is the best time to operate on patients diagnosed with ERM? This topic is still wide open for debate; thus, our debate today. While surgical intervention may be considered earlier in order to provide a better final VA in eyes with ERM, we need more studies to help us to better understand the importance of early vitrectomy in this group of patients. I have been assigned to argue for the side of operating at vision worse than 20/40. Let the debate begin!

Selected Readings

1. Harada C, Mitamura Y, Harada T. The role of cytokines and trophic factors in epiretinal membranes: involvement of signal transduction in glial cells. *Prog Retin Eye Res*. 2006; 25(2):149-164.
2. Dawson SR, Shunmugam M, Williamson TH. Visual acuity outcomes following surgery for idiopathic epiretinal membrane: an analysis of data from 2001 to 2011. *Eye (Lond)*. 2014; 28(2):219-224.

Late Breaking Developments, Part I

Panel Moderator: Robert L Avery MD

Panelists: Suber S Huang MD MBA, Mathew W MacCumber MD PhD, Shlomit Schaal MD PhD, and Diana V Do MD

NOTES

GATHER2 Phase 3 Efficacy Results

Arshad M Khanani MD, Sunil S Patel MD PhD, Giovanni Staurenghi MD, Ramin Tadayoni MD PhD, Carl J Danzig MD, David R Lally MD, Anat Loewenstein MD, David S Boyer MD, Glenn J Jaffe MD, Tien P Wong MD, Liansheng Zhu PhD, Julie Clark MD, Hersh Patel OD, and Carl D Regillo MD

I. Geographic Atrophy (GA)

A. GA is a late-stage form of AMD characterized by atrophy of retinal pigment epithelium, photoreceptors, and choriocapillaris.[1]

B. There are currently no approved treatments for GA.

C. Evidence suggests that the complement system plays a role in the development and progression of GA.[2,3]

II. Avacincaptad Pegol (ACP)

A. An investigational drug for the treatment of GA, ACP is a pegylated RNA aptamer that is administered through intravitreal injection.[4]

B. ACP binds to and inhibits complement C5, which prevents formation of complement fragments that play roles in inflammation and cell lysis.[4,5]

C. Through inhibition of C5, ACP may be able to slow the progression of GA.

III. Overview of GATHER1 Results

A. The Phase 2/3 GATHER1 study examined the efficacy and safety of monthly intravitreal injections of ACP in slowing the progression of GA.[4]

B. GATHER1 met the prespecified primary endpoint of mean rate of change in GA growth over 12 months. Reduction in the mean GA growth rate was 27.4% for ACP 2 mg and 27.8% for ACP 4 mg compared to corresponding sham groups over 12 months.[4]

C. Over 18 months, at least 1 ocular treatment–emergent adverse event in the study eye was reported for 63.6% of patients in the combined ACP groups and in 40.9% of patients in the combined sham groups.[6]

IV. GATHER2 Objectives and Study Design

A. GATHER2 is a Phase 3 study to evaluate the efficacy and safety of intravitreal injections of ACP in patients with GA.[7]

B. Approximately 400 patients were randomized 1:1 to monthly ACP 2 mg or sham. At Month 12, patients receiving monthly ACP 2 mg will be rerandomized to ACP 2 mg monthly or ACP 2 mg every other month, with final follow-up at Month 24.[7]

C. Enrollment criteria[6]

1. Key inclusion criteria

a. ≥50 years of age

b. Nonfoveal GA secondary to dry AMD

c. Total GA area ≥2.5 and ≤17.5 mm^2

d. If multifocal, at least 1 focal lesion should measure ≥1.25 mm^2

e. GA in part within 1500 microns of foveal center

2. Patients with disease inside and/or outside of the 1.5-mm diameter foveal area but not at the foveal center point were included.

3. Key exclusion criteria: Evidence of choroidal neovascularization in either eye at baseline

D. Endpoints[6]

1. Primary endpoint: Mean rate of growth (slope) estimated based on GA area in at least 3 timepoints (baseline, Month 6, and Month 12)

2. Key supportive endpoints

a. Mean change in BCVA from baseline to Month 12

b. Mean change in low luminance BCVA from baseline to Month 12

c. Mean change in visual function (NEI VFQ-25 score) from baseline to Month 12

V. GATHER2 Efficacy Results

A. Demographics and baseline characteristics

B. Topline efficacy results

VI. Conclusions

First-time efficacy results from the GATHER2 trial will be presented.

References

1. Fleckenstein M, Mitchell P, Freund KB, et al. The progression of geographic atrophy secondary to age-related macular degeneration. *Ophthalmology* 2018; 125(3):369-390.
2. Fritsche LG, Chen W, Schu M, et al. Seven new loci associated with age-related macular degeneration. *Nat Genet*. 2013; 45(4):433-439, 439e431-432.
3. Mullins RF, Schoo DP, Sohn EH, et al. The membrane attack complex in aging human choriocapillaris: relationship to macular degeneration and choroidal thinning. *Am J Pathol*. 2014; 184(11):3142-3153.
4. Jaffe GJ, Westby K, Csaky KG, et al. C5 inhibitor avacincaptad pegol for geographic atrophy due to age-related macular degeneration: a randomized pivotal Phase 2/3 trial. *Ophthalmology* 2021; 128(4):576-586.
5. Bajic G, Degn SE, Thiel S, Andersen GR. Complement activation, regulation, and molecular basis for complement-related diseases. *EMBO J*. 2015; 34(22):2735-2757.
6. Data on file. Iveric Bio.
7. ClinicalTrials.gov. A Phase 3 safety and efficacy study of intravitreal administration of Zimura (complement C5 inhibitor). www.clinicaltrials.gov/ct2/show/NCT04435366. Last update posted: Sept. 16, 2021.

GATHER2 Phase 3 Safety Results

Jeffrey S Heier MD, Arshad M Khanani MD MA, David A Eichenbaum MD, Charles C Wykoff MD PhD, Jason Hsu MD, Jordi Monés MD PhD, Jared S Nielsen MD, Frank Holz MD, Adnan Tufail MD, Glenn J Jaffe MD, Donald J D'Amico MD, Veeral S Sheth MD, Liansheng Zhu PhD, Julie Clark MD, Hersh Patel OD, and Peter K Kaiser MD

I. Avacincaptad Pegol (ACP)

ACP is a pegylated RNA aptamer that inhibits complement C5 and is aimed at slowing progression of geographic atrophy (GA) in patients.[1]

II. Overview of GATHER1 Findings

A. GATHER1 was a randomized, double-masked, sham-controlled, Phase 2/3 study that examined the safety and efficacy of monthly intravitreal injections of ACP in eyes with GA.[1]

B. A 27.4% reduction in mean GA growth rate was found with ACP 2 mg, and a 27.8% reduction was found with ACP 4 mg over 12 months compared to corresponding sham groups.[1]

C. Over 18 months, the majority of most commonly reported ocular treatment–emergent adverse effects (TEAE) in the study eye were associated with the intravitreal injection procedure.[2]

D. At least 1 ocular TEAE in the study eye was reported for 63.6% of patients in the combined ACP groups and 40.9% of patients in the combined sham groups over 18 months.[2]

E. There were no reported events of endophthalmitis in the study eye. Two patients were reported to have adverse events of intraocular inflammation in the study eye, which were mild and transient and not related to the injection procedure or study drug.[2]

1. One of these patients had iritis with visual acuity unchanged from the previous visit. No treatment was given for the iritis.[2]

2. The other patient had mild vitritis. Visual acuity was unchanged from baseline. No treatment was given for the vitritis.[2]

F. Over 12 months, choroidal neovascularization (CNV) was reported in the study eye for 2.7% in the sham group, 4% in the ACP 1 mg group, 9.0% in the ACP 2 mg group, and 9.6% in the ACP 4 mg group.[1] Over 18 months, CNV was reported in the study eye for 2.7% in the sham group, 7.7% in the ACP 1 mg group, 11.9% in the ACP 2 mg group, and 15.7% in the ACP 4 mg group.[2]

III. GATHER2 Study Design

A. GATHER2 is a randomized, double-masked, sham-controlled, Phase 3 study to evaluate the safety and efficacy of ACP in patients with GA.[3]

B. Patients enrolled had nonfoveal GA secondary to dry AMD in the study eye, which included lesions inside and/or outside the 1.5-mm diameter foveal area.[2]

C. Exclusion criteria included evidence of CNV in either eye at baseline.[2]

D. If patients developed wet AMD or CNV in the study eye during the trial and the diagnosis was confirmed, they remained in the trial and continued the study treatment with anti-VEGF therapy.[2]

IV. GATHER2 Safety Findings (Over 12 Months)

A. Demographics and baseline characteristics

B. Topline safety results

V. Conclusions

First-time safety results from the GATHER2 trial will be presented.

References

1. Jaffe GJ, Westby K, Csaky KG, et al. C5 inhibitor avacincaptad pegol for geographic atrophy due to age-related macular degeneration: a randomized pivotal Phase 2/3 trial. *Ophthalmology* 2021; 128(4):576-586.

2. Data on file. IVERIC bio.

3. ClinicalTrials.gov. A Phase 3 safety and efficacy study of intravitreal administration of Zimura (complement C5 inhibitor). www.clinicaltrials.gov/ct2/show/NCT04435366. Last update posted Sept. 16, 2021.

Treatment of Geographic Atrophy Secondary to AMD With Pegcetacoplan: Two-Year Outcomes From 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 can accompany lesion growth.[4]

FILLY

The FILLY trial, a randomized, 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.[6] 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.

Exudative AMD development was reported in 16% of monthly, 6% of EOM, and 1% of sham patients at 12 months; overall, a history of exudative AMD in the fellow eye and presence of a double layer sign at baseline in study eye were associated with an increased rate of exudative AMD development during the trial.[6]

DERBY and OAKS[7,8]

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.

Enrolled patients were ≥60 years of age, had a BCVA of ≥24 letters (approximate Snellen equivalent of 20/320), and a GA area between 2.5 and 17.5 mm^2, or if multifocal at baseline, at least 1 focal lesion ≥1.25 mm^2. The primary endpoint for both studies was change in GA lesion size via FAF imaging from baseline to Month 12. Safety measures included incidence of ocular and systemic adverse events. Secondary endpoints to be measured at Month 24 include BCVA, low luminance BCVA (LL-BCVA), low-luminance deficit, reading speed, NEI VFQ-25, Functional Reading Independence Index composite score, and microperimetry (OAKS only). GA lesion growth will be measured again at Month 24 as well.

OAKS and DERBY enrolled 637 and 621 patients, respectively. At Month 12 in OAKS, pegcetacoplan significantly reduced GA lesion growth vs. sham pooled in the monthly and EOM arms by 21% ($P = .0004$) and 16% ($P = .0055$), respectively. DERBY did not reach statistical significance; pegcetacoplan decreased GA lesion growth vs. sham by 12% ($P = .0609$) and 11% ($P = .0853$) in the monthly and EOM arms, respectively. Reductions were 16% ($P = .0001$, nominal) and 14% ($P = .0014$, nominal) in the monthly and EOM arms vs. sham in a prespecified pooled analysis. Most ocular adverse events in the study eye were considered mild or moderate. Exudative AMD rates in the pooled studies were 6.0%, 4.1%, and 2.4% for monthly, EOM, and sham pooled, respectively. The majority of intraocular inflammation cases were mild, and most patients resumed treatment. The rate of infectious endophthalmitis was consistent with other trials with intravitreal injections.

Results at Month 18 showed sustained reductions in the growth of GA lesions, with trends toward increasing efficacy over time. In OAKS, pegcetacoplan reduced GA lesion growth by 22% ($P < .0001$, nominal) and 16% ($P = .0018$, nominal) in monthly and EOM arms vs. sham pooled, respectively. In DERBY, pegcetacoplan reduced GA lesion growth by 13% ($P = .0254$, nominal) and 12% (P = .0332, nominal) in monthly and EOM arms vs. sham pooled, respectively. In a pooled analysis, reductions were 17% ($P < .0001$, nominal) in the monthly and 15% ($P = .0002$, nominal) in the pegcetacoplan EOM arms vs. sham pooled. The safety profile at Month 18 was consistent with observations at Month 12. Rates of investigator-determined exudative AMD through Month 18 were 9.5%, 6.2%, and 2.9% in the monthly, EOM, and sham pooled arms, respectively. Over 18 months, 21 events of intraocular inflammation were observed in 18 patients treated with pegcetacoplan.

At Month 24, additional analyses of the primary endpoint and the secondary functional endpoints will be presented. Additional safety at Month 24 will be presented.

References

1. Boyer DS, Schmidt-Erfurth U, van Lookeren Campagne M, Henry EC, Brittain C. The pathophysiology of geograhic atrophy secondary to age-related macular degeneration and the complement pathway as a therapeutic target. *Retina* 2017; 37:819-835.
2. Colijn JM, Buitendijk GHS, Prokofyeva E, et al. Prevalence of age-related macular degeneration in Europe: the past and the future. *Ophthalmology* 2017; 124:1753-1763.
3. Wong WL, Su X, Cheung CMG, et al. Global prevalence of age-related macular degeneration and disease burden projection for 2020 and 2040: a systematic review and meta-analysis. *Lancet Glob Health*. 2014; 2:e106-116.

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 secondary to age-related macular degeneration: a randomized Phase 2 trial. *Ophthalmology* 2020; 127(2):186-195.

6. Wykoff CC, Rosenfeld RJ, Waheed NK, et al. Characterizing new-onset exudation in the randomized Phase 2 FILLY trial of complement inhibitor pegcetacoplan for geographic atrophy. *Ophthalmology* 2021; 128(9):1325-1336.

7. ClinicalTrials.gov. Study to compare the efficacy and safety of intravitreal APL-2 therapy with sham injections in patients with geographic atrophy (GA) secondary to age-related macular degeneration. https://clinicaltrials.gov/ct2/show/NCT03525600. Last update posted June 21, 2021.

8. ClinicalTrials.gov. A study to compare the efficacy and safety of intravitreal APL-2 therapy with sham injections in patients with geographic atrophy (GA) secondary to age-related macular degeneration. https://clinicaltrials.gov/ct2/show/NCT03525613. Last update posted June 21, 2021.

SCORE2 5-Year Visual Acuity Results

Ingrid U Scott MD MPH

I. Background

A. Retinal vein occlusion is the most common retinal vascular disease after diabetic retinopathy. Macular edema is the most frequent cause of vision loss due to retinal vein occlusion.

B. The **S**tudy of **Co**mparative Treatments for **Re**tinal Vein Occlusion **2** (SCORE2), a Phase 3 randomized clinical trial funded by the National Eye Institute, demonstrated that bevacizumab is noninferior to aflibercept with respect to visual acuity after 6 months of monthly treatment in eyes with macular edema associated with central retinal vein occlusion (CRVO) or hemiretinal vein occlusion (HRVO).

C. At 6 months, SCORE2 participants with a protocol-defined good response were re-randomized to continued monthly treatment vs. a treat-and-extend (TAE) regimen of their originally assigned study drug; participants with a protocol-defined poor or marginal response were switched to an alternative treatment (treatment in eyes receiving monthly aflibercept was switched to dexamethasone implant and treatment in eyes receiving monthly bevacizumab was switched to aflibercept). One to 2 fewer injections of aflibercept or bevacizumab were administered in Months 6-12 to the TAE groups than to the monthly groups. With respect to visual acuity at Month 12, due to wide confidence intervals on the differences between the groups, caution is warranted before concluding the treatment regimens are associated with similar vision outcomes.

D. At 24 months postrandomization (12 months after cessation of the SCORE2 protocol-defined treatment schedule), participants initially randomized to aflibercept and those initially randomized to bevacizumab had similar visual acuity and central retinal thickness outcomes.

II. SCORE2 Long-term Follow-up Study (SCORE2 LTF)

A. Purpose: To investigate 5-year outcomes in eyes of SCORE2 participants initially treated with aflibercept or bevacizumab for macular edema due to CRVO or HRVO

B. Methods: SCORE2 participants were treated at investigator discretion after completing the 12-month treatment protocol and were followed-up to 60 months. Main outcomes are best-corrected electronic Early Treatment Diabetic Retinopathy Study (e-ETDRS) visual acuity letter score (VALS) and central subfield thickness (CST) on spectral domain OCT.

C. Results: Seventy-five percent of eligible participants (248/330) completed at least 1 visit between Months 24 and 60, and 45% (150/330) completed the Month 60 visit. Among participants who completed the Month 60 visit, overall mean VALS improvement over baseline was 13.5 (95% CI, 9.6-17.5), which is less than the mean improvement of 20.6 (95% CI, 18.7-22.4) observed at Month 12, with no significant differences between originally assigned study groups. Sixty-six percent of participants (99/150) received at least 1 treatment between Months 48 and 60, with a mean (SD) of 3.41 (3.69) treatments during this period. At Month 60, 83% of eyes had a CST less than 300 microns, and 24% had complete resolution of macular edema. Mean CST was 665 microns at baseline and 261 microns (95% CI, 241.2-280.9) at Month 60.

D. Conclusions: While VALS and CST improved substantially through Month 12, this improvement over baseline lessened during the second year, when treatment was at investigator discretion and fewer treatments were received. However, VALS and CST remained markedly improved over baseline through Year 5. The majority of patients continued to have macular edema and continued to be treated with anti-VEGF medication throughout the 5-year follow-up period. Continued monitoring and treatment at investigator discretion between Months 24 and 60 were successful in maintaining the significant VALS improvement among completers observed at Month 24 over baseline, irrespective of the original baseline treatment assignment. This 5-year outcomes analysis suggests that if continued monitoring and individualized treatment are provided for eyes with macular edema due to CRVO or HRVO, anti-VEGF therapy is associated with significant long-term visual acuity benefit (out to at least 5 years) compared with pretreatment visual acuity and is far superior to the untreated natural course of this condition.

Selected Readings

1. Scott IU, VanVeldhuisen PC, Ip MS, et al. SCORE2 report 2: study design and baseline characteristics. *Ophthalmology* 2017; 124:245-256.

2. Scott IU, VanVeldhuisen PC, Ip MS, et al. Effect of bevacizumab vs aflibercept on visual acuity among patients with macular edema due to central retinal vein occlusion: the SCORE2 randomized clinical trial. *JAMA* 2017; 317(20):2072-2087.

3. Scott IU, VanVeldhuisen PC, Ip MS, et al. Comparison of monthly vs treat-and-extend regimens for individuals with macular edema who respond well to anti-vascular endothelial growth factor medications: secondary outcomes from the SCORE2 randomized trial. SCORE2 report 6. *JAMA Ophthalmol*. 2018; 136(4):337-345.
4. Scott IU, Oden NL, VanVeldhuisen PC, et al. Month 24 outcomes after treatment initiation with anti-vascular endothelial growth factor therapy for macular edema due to central retinal or hemiretinal vein occlusion. SCORE2 report 10: a secondary analysis of the SCORE2 randomized clinical trial. *JAMA Ophthalmol*. 2019; 137(12):1389-1398.
5. Scott IU, VanVeldhuisen PC, Oden NL, et al. Month 60 outcomes after treatment initiation with anti-VEGF therapy for macular edema due to central or hemi-retinal vein occlusion. SCORE2 report 19. *Am J Ophthalmol*. 2022; 240:330-341.

DRCR Retina Network: Protocol AC Results

Aflibercept Monotherapy vs. Bevacizumab First Followed by Aflibercept if Needed for Treatment of Center-Involved Diabetic Macular Edema

Chirag D Jhaveri MD and the DRCR Retina Network

I. Background
   A. Diabetic macular edema (DME) is a leading cause of vision loss in working-age adults.[1,2]
   B. Intravitreous injection of anti-VEGF agents is the current standard treatment for DME.[1]
      1. Aflibercept and ranibizumab were FDA-approved.[3,4]
      2. Bevacizumab, a lower cost alternative, is used off-label.
   C. Due to the substantial differences in cost, an increasing number of insurers require "step therapy" wherein bevacizumab is used initially with a switch to another anti-VEGF agent if the clinical response is unsatisfactory.[6]
   D. Primary objective: To compare vision outcomes between treatment with aflibercept monotherapy vs. bevacizumab first followed by switching to aflibercept in eyes with a suboptimal response, for eyes with center-involved DME (CI-DME) and moderately impaired vision of 20/50 to 20/320.

II. Methods
   A. Study design: randomized multicenter clinical trial conducted by the DRCR Retina Network
      1. 270 patients (312 study eyes) were enrolled from 54 clinical sites in the United States and followed for 2 years.
      2. Eyes were randomly assigned in a 1:1 ratio to
         a. 2.0-mg intravitreous aflibercept ("aflibercept monotherapy")
         b. 1.25-mg intravitreous bevacizumab with a switch to 2.0-mg aflibercept if the eye met protocol criteria ("bevacizumab first")
      3. Primary outcome: average BCVA score over 2 years (area under the curve analysis)
   B. Major inclusion criteria
      1. Patients with type 1 or 2 diabetes, 18 years or older
      2. At least 1 eye with BCVA letter score between 69 and 24 (Snellen equivalent of 20/50 to 20/320)
      3. CI-DME on ophthalmoscopic examination
      4. Central subfield thickness (CST) values greater than OCT machine and sex specific thresholds[7,8]
   C. Major exclusion criteria
      1. Anti-VEGF treatment for DME in the past 12 months
      2. Any DME treatment within the prior 4 months
   D. Treatment
      1. Retreatment
         a. Injections administered if DME worsened or improved
         b. Injections deferred if sustained stability of visual acuity (VA) and retinal thickening achieved
      2. Switch criteria
         a. Starting from 12 weeks, eyes assigned to bevacizumab were switched to aflibercept if all prespecified criteria for suboptimal response were met.
            i. At 12, 16, and 20 weeks:
               (a) VA was 20/50 or worse,
               (b) VA did not improve ≥ 5 letters compared to or between each of the prior 1 visits,
               (c) OCT CST was above the eligibility thresholds,[7,8]
               (d) OCT CST did not improve ≥10% compared to or between each of the prior 2 visits, and
               (e) bevacizumab injections were given at the previous 2 consecutive visits.
            ii. Beginning at 24 weeks, eyes with a VA of 20/32 or worse meeting criteria (b) to (e) above
         b. Switched eyes received 2 monthly aflibercept injections, then continued with aflibercept injections according to the retreatment protocol.
   E. Visit schedule
      1. Year 1: every 4 weeks through 1 year
      2. Year 2: every 4 to 16 weeks depending on treatment course

III. Results

Results of this clinical trial that will be presented include the following:

A. Baseline participant and ocular characteristics

B. Study treatments

1. Mean number of study injections administered over 2 years
2. Percentage of eyes assigned to bevacizumab switched to aflibercept over 2 years

C. Efficacy

1. Primary outcome: average change in BCVA score over 2 years (area under the curve analysis)
2. Secondary outcomes
   a. VA outcomes at 24, 52, and 104 weeks
      i. Mean VA
      ii. Percentage of eyes ≥20/20, ≥20/40, or ≤20/200
      iii. Percentage of eyes improving ≥15 or ≥10 letters
      iv. Percentage of eyes worsening ≥10 or ≥15 letters
   b. Retinal thickening outcomes at 24, 52, and 104 weeks
      i. Mean OCT CST
      ii. Percentage of eyes with OCT CST below CI-DME threshold[7,8]
   c. Mean OCT retinal volume at 24, 52, and 104 weeks
   d. Diabetic retinopathy severity scores (DRSS) on fundus photographs at 52 and 104 weeks
      i. Percentage of eyes worsening ≥2 steps
      ii. Percentage of eyes improving ≥2 steps
   e. Complications of diabetic retinopathy through 2 years
      i. Percentage of eyes receiving panretinal photocoagulation
      ii. Percentage of eyes receiving vitrectomy
      iii. Percentage of eyes having vitreous hemorrhage
      iv. Percentage of eyes having traction retinal detachment
      v. Percentage of eyes having neovascularization of the iris
      vi. Percentage of eyes having neovascular glaucoma

D. Safety outcomes

1. Ocular
2. Systemic

IV. Conclusions

Conclusions will follow from the results presented.

References

1. Flaxel CJ, Adelman RA, Bailey ST, et al. Diabetic Retinopathy Preferred Practice Pattern. *Ophthalmology* 2020; 127(1):P66-P145.
2. Lee R, Wong TY, Sabanayagam C. Epidemiology of diabetic retinopathy, diabetic macular edema and related vision loss. *Eye Vis (Lond)*. 2015; 2:17.
3. Nguyen QD, Brown DM, Marcus DM, et al. Ranibizumab for diabetic macular edema: results from 2 Phase III randomized trials: RISE and RIDE. *Ophthalmology* 2012; 119(4):789-801.
4. Brown DM, Schmidt-Erfurth U, Do DV, et al. Intravitreal aflibercept for diabetic macular edema: 100-week results from the VISTA and VIVID studies. *Ophthalmology* 2015; 122(10):2044-2052.
5. 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.
6. Sachs RE, Kyle MA. Step therapy's balancing act: protecting patients while addressing high drug prices. *N Engl J Med*. 2022; 386(10):901-904.
7. Chalam KV, Bressler SB, Edwards AR, et al. Retinal thickness in people with diabetes and minimal or no diabetic retinopathy: Heidelberg Spectralis optical coherence tomography. *Invest Ophthalmol Vis Sci*. 2012; 53(13):8154-8161.
8. Writing Committee for the Diabetic Retinopathy Clinical Research Network; Gross JG, Glassman AR, Jampol LM, et al. Panretinal photocoagulation vs intravitreous ranibizumab for proliferative diabetic retinopathy: a randomized clinical trial. *JAMA* 2015; 314(20):2137-2146.

KSI-301 Anti-VEGF Antibody Biopolymer Conjugate for Retinal Vein Occlusion: Primary and Secondary 24-Week Efficacy and Safety Outcomes of the BEACON Phase 3 Pivotal Study

Michael A Singer MD on behalf of the KSI-301 BEACON RVO Study Group

Introduction

Intravitreal anti-VEGF therapy is the first-line approach for the treatment of macular edema (ME) secondary to retinal vein occlusion (RVO). The recommended treatment regimen for currently approved anti-VEGF medications is monthly dosing. Substantial functional and anatomic improvements can be achieved with these approved dosing regimens. However, the heavy treatment burden imposed on patients, caregivers, clinicians, and the health-care system is a significant barrier that can prevent good outcomes from being consistently achieved in the clinical setting.

KSI-301 is an antibody biopolymer conjugate (ABC) designed to provide potent, safe, and longer-lasting intraocular VEGF suppression. The ABC platform leverages the unique biophysical properties of branched phosphorylcholine biopolymers to maintain effective therapeutic levels of a biologic, such as an anti-VEGF antibody, for longer periods of time inside the eye. A comprehensive development program with pivotal studies evaluating the potential of KSI-301 as a treatment option for patients with wet AMD, diabetic macular edema, RVO, and nonproliferative diabetic retinopathy is underway.

The objective of the Phase 3 BEACON study is to demonstrate that KSI-301 is noninferior to aflibercept while providing a clinically meaningful reduction in treatment burden for patients with ME secondary to RVO.

Methods

Treatment-naïve patients with ME secondary to branch or central RVO were randomized 1:1 into 2 treatment arms: aflibercept dosed monthly or KSI-301 every 8 weeks (q8w) after 2 initial monthly doses. The primary efficacy endpoint is the mean change in BCVA at Week 24 (see Figure 1). Secondary endpoints at Week 24 include change from baseline in retinal thickness measured by OCT, central subfield thickness (CST), the proportions of patients gaining or losing ≥10 or ≥15 ETDRS letters from baseline, and the incidence of ocular and non-ocular adverse events. Starting at Week 24 through the end of the study, patients in both treatment arms are evaluated monthly and treated according to protocol-defined disease activity criteria.

Results

134 sites across the United States, Europe, and Israel randomized 568 patients (279 females, 49.1%) into the study with a mean age of 65.3 years. At baseline, mean BCVA was 60.4 letters, with 32% of patients having a Snellen equivalent of 20/40 or better; mean baseline CST was 577.4 µm. Results for the primary endpoint and additional secondary endpoints will be presented at the meeting.

Conclusions

Patients with treatment-naïve ME secondary to RVO can achieve substantial improvements in function and anatomy with monthly dosing of currently available anti-VEGF therapies. However, this high treatment burden prevents a significant proportion of patients from achieving and maintaining these outcomes in the clinical setting. KSI-301 has the potential to address this unmet medical need. Data on the Week 24 primary and secondary efficacy outcomes will be presented at the meeting.

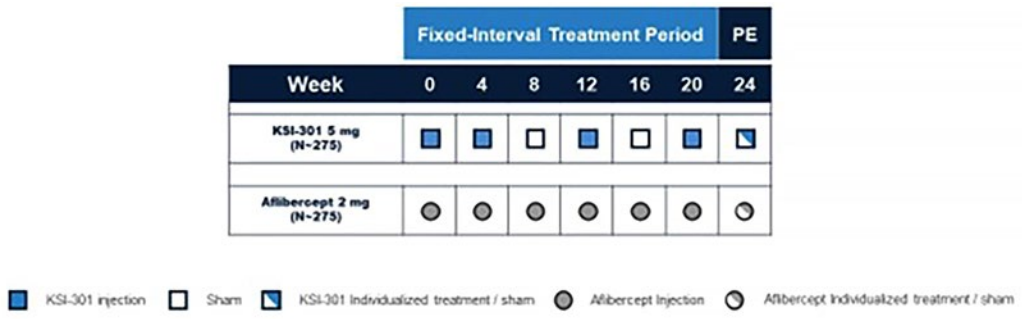

Figure 1. Phase 3 BEACON Study schematic design, first 24 weeks.

Update on OCT Angiography

Nadia K Waheed MD

OCT angiography is being used in clinic and in clinical trials to elucidate the state of the retinal and choroidal vessels in health and disease. This presentation will focus on technological advancements in OCT-A and its utility in the retinal clinic, in clinical trials, and in retinal research. It will also look at some of the systemic clinical trials that incorporate OCT-A and what retinal and choroidal vessels can teach us about systemic disease and aging.

Can We Use OCT Angiography Instead of Fluorescein Angiography for Nonproliferative Diabetic Retinopathy Evaluation and PDR Detection?

Ramin Tadayoni MD PhD

Why This Comparison?

Fluorescein angiography (FA) and more recently OCT angiography (OCT-A) are both used to evaluate retinal vessels and their abnormalities. Retinal vessel abnormalities are considered as the main hallmark of the pathophysiology of diabetic retinopathy (DR). While color photography (CP) is used for DR screening, FA has been for years the second-line exam to better evaluate the risk of complication by revealing nonperfusion areas (NP) or already existing neovascularization (NV). As OCT-A is noninvasive, it is legitimate to ask ourselves whether it can be used instead of FA as second line. OCT-A could even replace CP for first-line evaluation of DR, as it has been shown to be in theory superior to CP, and its integration with structural OCT can also allow screening for diabetic macular edema (DME) at the same time.

In Research Conditions

Several studies have compared OCT-A to FA and consistently showed that OCT-A is at least equal or often superior to FA for diagnosis of NP or NV and other DR abnormalities, such as microaneurysms or intraretinal microvascular abnormalities. Several parameters measured on OCT-A have been shown also to correlate well with DR stages or have been suggested as being able to predict risk of complication.

Nowadays, many DR patients are treated with intravitreal injections, mostly for DME. As we have shown in a previous work, OCT-A may even be more powerful than CP and FA in properly evaluating DR, NP, or NV evolution in these patients.

However, with ultrawide-field (UWF) machines FA can today explore up to 80% of the retinal surface. Commercial OCT-A is still unable to cover the same area. OCT-A machines in most practices today can cover 6×6-mm areas, and doing montages to achieve larger areas is difficult and time consuming. The field covered by a single cube of OCT-A has, however, increased with time to 9, 12, and then 15 mm and even 23 mm in recent machines. However, the largest fields often come at the cost of some lowering of resolution and they still cover less than the UWF FA. Several papers have suggested that this may not be a problem, as the field may be enough for most cases in theoretical models or more subtle parameters only measurable on OCT-A, as selective studies of capillary layers, state of the foveal avascular zone, vascular geometry (fractal dimension, tortuosity, or acircularity), or even choriocapillaris vascular nonperfusion can help overcome the field issue and allow indirect evaluation of DR.

In a recent work we aimed to explore OCT-A NP area using wide-field OCT-A (montage of five 12×12-mm images) in eyes with 2 distinctive stages of DR, with and without neovascularization. Interestingly, we noticed that in 17% of eyes, the NV were outside the traditional 7 ETDRS fields and were not visible on OCT-A. As NV happened close to NP areas, in these eyes, the NP was also mainly outside the field of OCT-A, with the measured NP surface area far below the theoretical cutoff to distinguish proliferative from nonproliferative DR. In other words, in these eyes the 2 parameters that a naked eye can evaluate on OCT-A, presence or not of NV and extent of NP, may have failed to diagnose presence of NV due to insufficient field compared to UWF imaging.

In Clinical Practice

In clinical practice we would appreciate the absence of risk and ease of use of OCT-A: no need to be able and have the material to treat allergies or resuscitate a shock. Patients seem also to prefer OCT-A to FA, which requires an injection. Concerning the reading of images, one should consider the quality of the images, which may be variable from machine to machine or eye to eye with OCT-A, as with FA. While most ophthalmologists are familiar with FA, and the fluorescence of NV often makes it shine and be visible even on printed images, analysis of OCT-A may need proper segmentation to visualize the NV, making use of the appropriate viewer and screen mandatory. OCT-A, on the other hand, is much more potent compared to CP and FA, in properly showing abnormalities and their evolution in eyes with intravitreal injections. The field of view should never be forgotten, and apart from screening for DR, for the diagnosis of DR stages at least the 7 field ETDRS area should be covered with both techniques, and a combination of exams, such as UWF CP and OCT-A, can be used to explore an even larger portion of the retina.

EviRed, a Research Program That Tries to Answer These Questions

Clearly, the number of factors to integrate to find the best ways to evaluate DR is very high. Moreover, the best parameters for evaluating DR may not be easily visible by the naked eye. To be able to help address comprehensively the problem of modern DR evaluation, we have designed a French national research program that will include thousands of diabetic patients followed up for several years, using modern imaging, from UWF imaging to OCT-A, and the use of artificial intelligence for the analyzes. We hope that it will be helpful and that its large database will stimulate collaboration. For more information, see www.evired.org.

Conclusion

For those involved in research on DR, it is quite obvious that OCT-A has a high potential to become the keystone of DR evaluation in the future. In our everyday practice today, if properly used, OCT-A can replace FA as the second line for DR evaluation and NV detection or even the first line in combination with CP. Its limits, in particular in terms of field, should be taken into account, and FA or UWF FA may still be useful in some cases.

Selected Readings

1. Cui Y, Zhu Y, Wang JC, et al. Comparison of widefield swept-source optical coherence tomography angiography with ultra-widefield colour fundus photography and fluorescein angiography for detection of lesions in diabetic retinopathy. *Br J Ophthalmol*. 2021; 105(4):577-581.
2. Sawada O, Ichiyama Y, Obata S, et al. Comparison between wide-angle OCT angiography and ultra-wide field fluorescein angiography for detecting non-perfusion areas and retinal neovascularization in eyes with diabetic retinopathy. *Graefes Arch Clin Exp Ophthalmol*. 2018; 256(7):1275-1280.
3. Hirano T, Kakihara S, Toriyama Y, Nittala MG, Murata T, Sadda S. Wide-field en face swept-source optical coherence tomography angiography using extended field imaging in diabetic retinopathy. *Br J Ophthalmol*. 2018; 102(9):1199-1203.
4. Ong JX, Konopek N, Fukuyama H, Fawzi AA. Deep capillary nonperfusion on OCT angiography predicts complications in eyes with referable nonproliferative diabetic retinopathy. *Ophthalmol Retina*. Epub ahead of print 2022 July 5; S2468-6530(22)00336-0. doi: 10.1016/j.oret.2022.06.018.
5. Couturier A, Rey PA, Erginay A, et al. Widefield OCT-angiography and fluorescein angiography assessments of nonperfusion in diabetic retinopathy and edema treated with anti-vascular endothelial growth factor. *Ophthalmology* 2019; 126(12):1685-1694.
6. Russell JF, Flynn HW Jr, Sridhar J, et al. Distribution of diabetic neovascularization on ultra-widefield fluorescein angiography and on simulated widefield OCT angiography. *Am J Ophthalmol*. 2019; 207:110-120.
7. Fayed AE, Abdelbaki AM, El Zawahry OM, Fawzi AA. Optical coherence tomography angiography reveals progressive worsening of retinal vascular geometry in diabetic retinopathy and improved geometry after panretinal photocoagulation. *PLoS One* 2019; 14(12):e0226629.
8. Nesper PL, Roberts PK, Onishi AC, et al. Quantifying microvascular abnormalities with increasing severity of diabetic retinopathy using optical coherence tomography angiography. *Invest Ophthalmol Vis Sci*. 2017; 58(6):BIO307-BIO315.

Home OCT

Nancy M Holekamp MD

Introduction

Wet AMD is the leading cause of blindness in the United States. Multiple approved anti-VEGF therapies have given patients hope of maintaining their vision. However, requirements for high frequency of these treatments is burdensome for both patients and doctors.

AI-powered home-based digital health techniques are promising a new era of personalized medicine. Home-based OCT is a major step in that direction for AMD patients. OCT has been an indispensable tool for guiding AMD therapy and understanding its progression over the last two decades. OCT provides invaluable spatial information by giving a 3-D view and cross-sections of the retina and specifically of retinal fluid, the target for anti-VEGF drugs. However, temporal granularity of this high-resolution technique is limited, as it can only be performed in the office using relatively expensive machines through trained operators.

Notal Vision Home OCT (NVHO) may potentially overcome these limitations through a home-based self-imaging OCT device, AI-powered algorithms, and a monitoring center to guide the process and patient journey.

We conducted a study with wet AMD patients to understand the technical performance, patient compliance, and patient satisfaction with this method of home monitoring.

Methods

Fifteen patients undergoing anti-VEGF therapy for wet AMD in at least 1 eye were enrolled for this study. The participants were not given any in-office training and only verbal information about the home OCT. The patients were courier-delivered the device directly from a central monitoring center and were supported by an onboarding call from the monitoring center. The patients were able to call the monitoring center during the study as needed. The participants were instructed to perform daily self-scanning for a period of 3 months. The scans were uploaded to the cloud and analyzed using an artificial intelligence tool called the Notal OCT Analyzer (NOA). The scans were also graded by human experts and evaluated by human experts for fluid presence and compared with in-office OCT scans. The collected data was further analyzed by NOA to produce retinal thickness maps and fluid quantification measurements.

Figure 1. Home use OCT device.

The outcomes measured related to scanning performance included agreement between NVHO and in-office OCT scans as graded by human readers for the presence of fluid. In addition, agreement between NOA on NVHO scans and human experts on in-office scans for fluid presence in the retinal images of the same patient was recorded. The self-imaging performance was measured using weekly self-scan rate, percentage of successfully completed scans, image quality of acquired images, and total time to scan. In addition, patients were given a questionnaire at the end of the program to provide feedback regarding their overall experience with the program.

The analysis compared traditional retinal thickness maps and NOA-based fluid volumes.

Results

NVHO scans analyzed by NOA and in-office OCT scans graded by human experts agreed on the fluid status in 96% of cases.

NOA and human experts agreed on the fluid status in 83% of NVHO scans, and discrepancies were limited to trace amounts of fluid. The mean weekly scan frequency was 5.7 ± 0.9 scans per week, and 93% of scans were eligible for NOA analyses. Mean scan time was 42 seconds. The results from a patient survey showed that over 97% of the patients found the daily testing convenient and self-testing easy to perform.

The results of fluid volume quantification and retinal thickness were compared. In Figure 2 we demonstrate the poor correlation between these biomarkers ($P < .000001$). Figure 3 illustrates fluid volume trajectory of a patient undergoing anti-VEGF therapy.

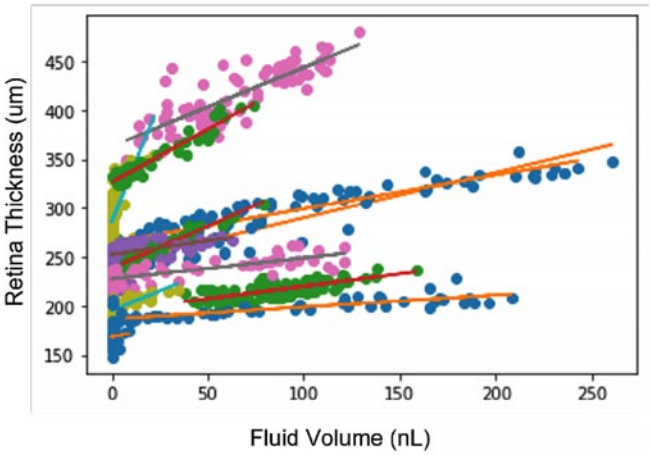

Figure 2. Lack of correlation between fluid volume and retinal thickness.

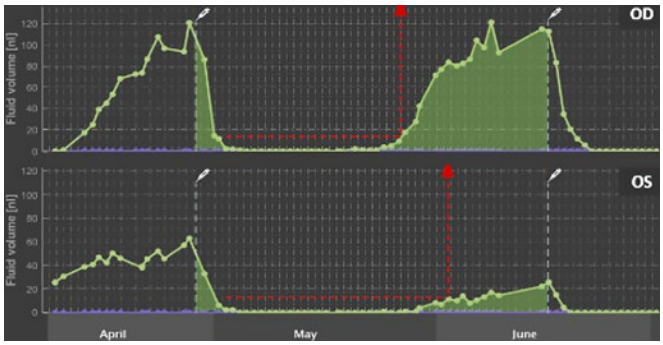

Figure 3. Fluid volume trajectories demonstrate how prescheduled treat-and-extend office visits can expose the retina to extensive fluid.

Conclusions

Daily home OCT imaging is feasible among patients with neovascular AMD. It demonstrated good agreement with human expert grading for retinal fluid identification and excellent agreement with in-clinic OCT scans. Home OCT allows for detailed graphical and mathematical analyses of retinal fluid volume trajectories, including novel parameters to inform clinical decision making.

Selected Reading

1. Liu YL, Holekamp N, Heier JS. Prospective, longitudinal study: daily self-imaging with home OCT in neovascular age-related macular degeneration. *Ophthalmol Retina*. Epub ahead of print 2022 Feb 28; S2468-6530(22)00073-2. doi: 10.1016/j.oret.2022.02.011.

Update on Intraoperative OCT

Lejla Vajzovic MD, Jianwei D Li, William Raynor, Al-Hafeez Dhalla PhD, Christian Viehland PhD, Robert Trout, Joseph A Izatt PhD, and Cynthia A Toth MD

Perioperative OCT

With the translation of OCT to ophthalmology, some of the earliest uses were in preoperative surgical planning and postoperative monitoring of macular diseases such as macular holes, epiretinal membranes, tractional retinal detachment, diabetic macular disease, myopic schisis, and retinal detachment. For surgical planning, OCT imaging revealed cross-sectional macular details that were not available from other modalities, such as photography or ophthalmoscopy. After surgery, OCT was used to examine for the closure of macular holes and subretinal or intraretinal fluid and persisting membranes or traction.[1-4] Absence of feedback during surgery limited the use of OCT to assure achieving surgical endpoints.

Handheld OCT During Surgical Pauses

Technological development, intraoperative applications, and translational challenges

Intraoperative OCT was first achieved with handheld systems, with later use of attachments to suspend an OCT handpiece on the side of the microscope or an armature to stabilize and suspend an OCT scanning head over the eye.[5-9]

Intraoperative OCT (iOCT) provides novel information during surgery, such as the absence of membranes across the macular surface after peeling, change in contour of a macular hole or the location of subretinal fluid or of an elevated curl of internal limiting membrane during surgery.[10-17]

Ophthalmic microsurgery has to be halted to move the OCT scanning optics over the patient's eye; thus, the information cannot be used in real time during an operation. Additional surgical time is therefore required to pause for imaging.

Live 2-D OCT Imaging in Surgery

Technological development, intraoperative applications, and translational challenges

Incorporating optical systems within the viewing path of the operating microscope enables OCT imaging during surgical maneuvers. Microscope-integrated OCT (MI-OCT) systems using spectral domain OCT (SD-OCT) allowed capture of live 2-D OCT imaging during surgery and subsequent viewing of 3-D volumes, usually on an external screen, at pauses in surgery.[18-20] These have rapidly evolved to options of viewing the OCT images with a monitor adjacent to the microscope and to include a monocular heads-up display within the surgical eyepiece for intrasurgical viewing of 2-D images by the surgeon.[19]

MI-OCT has been used for review and analysis at pauses between surgery and for real-time 2-D viewing of surgical instrument–tissue interactions in systems with heads-up display. The heads-up viewing of surgery with live 2-D iOCT is a revolutionary adjunct to the decades-old conventional surgical view with transpupillary or endoillumination of the retinal surface with visible light. Studies have shown multiple uses of iOCT information, such as to assess completeness of peel or presence of macular hole or subretinal fluid, and an impact of such information on surgical decision making.[22-25]

With visualization of live 2-D B-scans, it is difficult to maintain a view of an instrument and surgical tissue during the range of a surgical motion (eg, as the surgeon peels a membrane); it can be challenging to maintain the area of interest within the location of the B-scans; and surgical instruments produce shadows. Image size, pixel resolution, and contrast within the microscope oculars are limited compared to those on an external screen, and one cannot view images in full 3-D via a monocular heads-up display. Integrating instruments and iOCT technology will be important to overcome these challenges.[26]

Live 3-D OCT Imaging of Surgery

Technological development, intraoperative applications, and translational challenges

An investigational custom ultrafast swept source OCT (SS-OCT) system integrated into a microscope mechanical interface with custom graphic processing unit software has resulted in the first system capable of live MI-OCT imaging of 3-D volumes.[27] Linking the 3-D iOCT volume capture to projection via stereoscopic heads-up display (in both microscope oculars) has been described as "4-D MI-OCT."[28,29]

Under approved research protocols, the 4-D MI-OCT investigational system enables stereoscopic surgeon viewing of near real-time 3-D iOCT during retinal surgery for macular hole, epiretinal membrane, and diabetic traction detachments. Furthermore, in research applications in the laboratory, surgical maneuvers can be performed/visualized by 4-D iOCT alone, without the use of the conventional microscope view. Studies have shown a benefit of iOCT in resident training and the utility of iOCT information in vitreoretinal surgery.[30,31]

With current improvements in capture and processing speeds, 4-D iOCT technology has reached the speed necessary for video-rate volumetric viewing. While stereoscopic viewing has been achieved within the microscope oculars, image size, pixel resolution, and contrast within the microscope oculars remain limited compared to those on an external screen. Fast imaging speeds and a high signal-to-noise ratio enabled by a SS 4-D iOCT technology allows for greater visualization of surgical maneuvers.[32-36] Furthermore, with recent visualization and quantification methods of subretinal drug delivery, 4-D iOCT enables surgeons to evaluate the success of subretinal drug delivery performed.[35-36] However, instrument shadowing, field of view, and surgical viewpoint limit the full utilization of 4-D iOCT.

The 4-D iOCT is positioned to inform surgical procedures that are not currently achievable with conventional surgical imaging. Future development of faster iOCT systems, OCT compatible instruments, and refinements to control surgeon viewpoint will improve iOCT volumetric visualization of the vitreoretinal interface, retinal surface, and retinal and subretinal structures. This provides a unique opportunity to improve surgical outcomes.

References

1. Wilkins JR, Puliafito CA, Hee MR, et al. Characterization of epiretinal membranes using optical coherence tomography. *Ophthalmology* 1996; 103(12):2142-2151.
2. Mikajiri K, Okada AA, Ohji M, et al. Analysis of vitrectomy for idiopathic macular hole by optical coherence tomography. *Am J Ophthalmol*. 1999; 128(5):655-657.
3. Gallemore RP, Jumper MJ, McCuen BW, Jaffe GJ, Postel EA, Toth CA. Diagnosis of vitreoretinal adhesions in macular disease with optical coherence tomography. *Retina* 2000; 20(2):115-120.
4. Massin P, Allouch C, Haouchine B, et al. Optical coherence tomography of idiopathic macular epiretinal membranes before and after surgery. *Am J Ophthalmol*. 2000; 130(6):732-739.
5. Dayani PN, Maldonado R, Farsiu S, Toth CA. Intraoperative use of handheld spectral domain optical coherence tomography imaging in macular surgery. *Retina* 2009; 29(10):1457-1468.
6. Ray R, Barañano DE, Fortun JA, et al. Intraoperative microscope-mounted spectral domain optical coherence tomography for evaluation of retinal anatomy during macular surgery. *Ophthalmology* 2011; 118(11):2212-2217.
7. Pichi F, Alkabes M, Nucci P, Ciardella AP. Intraoperative SD-OCT in macular surgery. *Ophthalmic Surg Lasers Imaging*. 2012; 43(6):54-60.
8. Riazi-Esfahani M, Khademi M, Mazloumi M, Khodabandeh A, Riazi-Esfahani H. Macular surgery using intraoperative spectral domain optical coherence tomography. *J Ophthalmic Vis Res*. 2015; 10(3):309.
9. Branchini LA, Gurley K, Duker JS, Reichel E. Use of handheld intraoperative spectral-domain optical coherence tomography in a variety of vitreoretinal diseases. *Ophthalmic Surg, Lasers Imaging*. 2016; 47(1):49-55.
10. Scott AW, Farsiu S, Enyedi LB, Wallace DK, Toth CA. Imaging the infant retina with a hand-held spectral-domain optical coherence tomography device. *Am J Ophthalmol*. 2009; 147(2):364-373.
11. Wykoff CC, Berrocal AM, Schefler AC, Uhlhorn SR, Ruggeri M, Hess D. Intraoperative OCT of a full-thickness macular hole before and after internal limiting membrane peeling. *Ophthalmic Surg, Lasers Imaging*. 2010; 41(1):7-11.
12. Henry CR, Berrocal AM, Hess DJ, Murray TG. Intraoperative spectral-domain optical coherence tomography in Coats' disease. *Ophthalmic Surg Lasers Imaging*. 2012; 43;e80-e84.
13. Ehlers JP, Dupps WJ, Kaiser PK, et al. The Prospective Intraoperative and Perioperative Ophthalmic Imaging With Optical Coherence Tomography (PIONEER) study: 2-year results. *Am J Ophthalmol*. 2014; 158(5):999-1007.
14. Ehlers JP, Xu D, Kaiser P, Singh R, Srivastava S. Intrasurgical dynamics of macular hole surgery: an assessment of surgery-induced ultrastructural alterations with intraoperative optical coherence tomography. *Retina* 2014; 34(2):213-221.
15. Ehlers JP, Tam T, Kaiser P, Martin D, Smith G, Srivastava S. Utility of intraoperative optical coherence tomography during vitrectomy surgery for vitreomacular traction syndrome. *Retina* 2014; 34(7):1341-1346.
16. Ehlers JP, Ohr MP, Kaiser PK, Srivastava SK. Novel microarchitectural dynamics in rhegmatogenous retinal detachments identified with intraoperative optical coherence tomography. *Retina* 2013; 33:1428-1434.
17. Ehlers JP, Han J, Petkovsek D, Kaiser PK, Singh RP, Srivastava SK. Membrane peeling-induced retinal alterations on intraoperative OCT in vitreomacular interface disorders from the PIONEER study. *Invest Opthalmol Vis Sci*. 2015; 56(12):7324-7330.
18. Tao YK, Ehlers JP, Toth CA, Izatt JA. Intraoperative spectral domain optical coherence tomography for vitreoretinal surgery. *Opt Lett*. 2010; 35(20):3315-3317.
19. Ehlers JP, Tao YK, Farsiu S, Maldonado R, Izatt JA, Toth CA. Integration of a spectral domain optical coherence tomography system into a surgical microscope for intraoperative imaging. *Invest Ophthalmol Vis Sci*. 2011; 52(6):3153-3159.
20. Binder S, Falkner-Radler CI, Hauger C, Matz H, Glittenberg C. Feasibility of intrasurgical spectral-domain optical coherence tomography. *Retina* 2011; 31(7):1332-1336.
21. Tao YK, Srivastava SK, Ehlers JP. Microscope-integrated intraoperative OCT with electrically tunable focus and heads-up display for imaging of ophthalmic surgical maneuvers. *Biomed Opt Express*. 2014; 5(6):1877-1885.
22. Hahn P, Migacz J, O'Connell R, et al. Preclinical evaluation and intraoperative human retinal imaging with a high-resolution microscope-integrated spectral domain optical coherence tomography device. *Retina* 2013; 33(7):1328-1337.
23. Ehlers JP, Kaiser PK, Srivastava SK. Intraoperative optical coherence tomography utilizing the RESCAN 700: preliminary results from the DISCOVER study. *Br J Ophthalmol*. 2014; 98(10):1329-1332.
24. Ehlers JP, Goshe J, Dupps WJ, et al. Determination of feasibility and utility of microscope-integrated optical coherence tomography during ophthalmic surgery: the DISCOVER study RESCAN results. *JAMA Ophthalmol*. 2015; 133(10):1124-1132.
25. Pfau M, Michels S, Binder S, Becker MD. Clinical experience with the first commercially available intraoperative optical coherence tomography system. *Ophthalmic Surg Lasers Imaging Retina*. 2015; 46(10):1001-1008.
26. Ehlers JP, Srivastava SK, Feiler D, Noonan AI, Rollins AM, Tao YK. Integrative advances for OCT-guided ophthalmic surgery and intraoperative OCT: microscope integration, surgical instrumentation, and heads-up display surgeon feedback. *PLoS One*. 2014; 9(8):e105224.
27. Carrasco-Zevallos OM, Keller B, Viehland C, et al. Real-time 4D visualization of surgical maneuvers with 100 kHz swept-source microscope integrated optical coherence tomography (MIOCT) in model eyes. *Invest Ophthalmol Vis Sci*. 2014; 55(13):1633.
28. Viehland C, Keller B, Carrasco-Zevallos OM, et al. Enhanced volumetric visualization for real time 4D intraoperative ophthalmic swept-source OCT. *Biomed Opt Express*. 2016; 7(5):1815-1829.
29. Shen L, Carrasco-Zevallos OM, Keller B, et al. Novel microscope-integrated stereoscopic heads-up display for intrasurgical optical coherence tomography. *Biomed Opt Express*. 2016; 7(5):1711-1726.
30. Todorich B, Shieh C, DeSouza PJ, et al. Impact of microscope-integrated OCT on ophthalmology resident performance of anterior segment surgical maneuvers in model eyes. *Invest Ophthalmol Vis Sci*. 2016; 57(9):OCT146-153.
31. Carrasco-Zevallos OM, Keller B, Viehland C, et al. Optical coherence tomography for retinal surgery: perioperative analysis to real-time four-dimensional image-guided surgery. *Invest Ophthalmol Vis Sci*. 2016; 57(9):OCT37-50.

32. Grewal DS, Bhullar PK, Pasricha ND, et al. Intraoperative 4-dimensional microscope-integrated optical coherence tomography-guided 27-gauge transvitreal choroidal biopsy for choroidal melanoma. *Retina* 2017; 37(4):796-799.

33. Gabr H, Chen X, Zevallos-Carrasco OM, et al. Visualization from intraoperative swept-source microscope-integrated optical coherence tomography in vitrectomy for complications of proliferative diabetic retinopathy. *Retina* 2018; 38(suppl 1):S110-S120.

34. Vajzovic L, Sleiman K, Viehland C, et al. Four-dimensional microscope-integrated optical coherence tomography guidance in a model eye subretinal surgery. *Retina* 2019; 39(suppl 1):S194-S198.

35. Song Z, Xu L, Wang J, et al. Lightweight learning-based automatic segmentation of subretinal blebs on microscope-integrated optical coherence tomography images. *Am J Ophthalmol.* 2021; 221:154-168.

36. Sastry A, Li JD, Raynor W, et al. Microscope-integrated OCT-guided volumetric measurements of subretinal blebs created by a suprachoroidal approach. *Transl Vis Sci Technol.* 2021; 10(7):24.

Imaging the Vitreous

A Novel Method of Imaging the Vitreous With Boosted OCT

Richard F Spaide MD

The vitreous is an enigmatic structure. It is by necessity transparent, but it participates in many vision-threatening disorders. By being transparent it is very difficult to visualize by ophthalmoscopy or image by photography or OCT. The chief methods of examining the vitreous as a structure have involved dissection techniques that remove the outer coats of the eye to expose the vitreous body. By default, the interaction between the vitreous and the retina are destroyed in the process. Because the vitreous is optically clear, the reflectance data are sparse in optical imaging modalities. This includes OCT to the extent that the vitreous cavity has such a low signal level it has been used as the background in contrast to noise calculations. To improve the process, we found that when averaging 4 A-scans prior to the Fourier transform, the boosted image contained sufficient information to allow proper registration. With this form of enhanced vitreous imaging, we could obtain 100 scans per section of the vitreous and then average those. The averaged B-scan was then enhanced by gamma compression and tone mapping to increase the brightness and local contrast in the areas of low signal (the vitreous) while preserving details in the retina. The images were evaluated with volume rendering.

The premacular bursa and area Martegiani were readily visualized in 3 dimensions. Every subject older than the third decade of life, including 1 in the third decade, showed signs of vitreous degeneration with formation of vitreous cavitation. Important hallmarks of this degeneration were areas of liquefaction of the vitreous and regions of vitreous condensation bordering these areas. The internal aspects of the image block showed a patterning, with a banding pattern radiating toward the superior aspect of the premacular bursa as it turned anteriorly. There were areas of optically empty vitreous, implying vitreous synchysis bordered by syneresis. The condensed vitreous at the border of the cisterns were punctate, linear, or in advanced cases, plate- or sheet-like. Greater amounts of liquefaction seemed bordered by more prominent condensations, and the patterns of vitreous changes demonstrated shared similarities in patterns. The upper aspects of these areas of clearing were not visible in the limited depth of the scans.

The vitreous cortex is estimated to be at least 100 micrometers thick, but the only discernable change in the eyes of younger patients is a hazy zone of increased reflectivity in the vitreous. The inner border of the poorly defined zone of increased reflectivity was contiguous with a comparatively better-defined region of hyperreflectivity. This cortical vitreous condensation was visible in every eye to some extent and was more prominent in older eyes. Between the cortical vitreous condensation and the surface of the retina, a darker, hyporeflective region is seen. When viewed on edge, this zone is not transparent, indicating that vitreous is still present. In areas where the vitreous was detaching from the macula, tears in the posterior vitreous could be seen, with disgorgement of the fluid from the premacular bursa to the subhyaloid face. In cases with a posterior vitreous detachment, a round defect could be seen in the posterior vitreous face. The relative fragility of the vitreous cortex in the macular region may be a design feature, as it could spare the central macula from tractional forces that occur with posterior vitreous detachment.

Selected Readings

1. Worst JGF, Los LI. *Cisternal Anatomy of the Vitreous*. Kugler Publications; 1995.
2. Eisner G. Slitlamp examination of the vitreous in autopsy eyes: I. Autopsy technique and examination method. *Graefes Arch Clin Exp Ophthalmol*. 1971; 182(1):1-7.
3. Sebag J. *The Vitreous: Structure, Function, and Pathobiology*. Springer-Verlag; 1989.
4. Spaide RF, Valmaggia P, Maloca PM, et al. Imaging the vitreous with a novel boosted optical coherence tomography technique: vitreous degeneration and cisterns. *Retina*. Epub ahead of print 2022 Mar 17. doi: 10.1097/IAE.0000000000003474.
5. Spaide RF, Valmaggia P, Maloca PM. Imaging the vitreous with a novel boosted optical coherence tomography technique: posterior vitreous detachment. *Retina*. Epub ahead of print 2022 Apr 13. doi: 10.1097/IAE.0000000000003500.

Mitochondrial Imaging Insights Into Retinal Diseases

Rishi P Singh MD

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Imaging Panel Discussion

Panel Moderator: Jay S Duker MD

Panelists: Marion Ronit Munk MD PhD, Giuseppe Querques MD, Nadia Khalida Waheed MD and Sandrine Zweifel MD

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Late Breaking Developments, Part II

Panel Moderator: Sharon D Solomon MD

Panelists: Rajendra S Apte MD PhD, Catherine A Cukras MD PhD, Sunir J Garg MD FACS, and Hendrik P Scholl MD

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Management of Non-neovascular Fluid in AMD: Observe and Extend

David Sarraf MD

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Port Delivery System Long-term Portal Extension Data: Three-Year Follow-up From the Phase 3 Archway Study

Carl D Regillo MD FACS

Background

Neovascular AMD (nAMD) remains a leading cause of blindness despite widespread use of intravitreal anti-VEGF treatment.[1-3] Optimal long-term use of anti-VEGF monotherapy is dependent on frequent injections and visits for patient monitoring,[1,3-6] which can place a high burden on patients, their caregivers, and health-care providers.[7-10] The Port Delivery System with ranibizumab (PDS; Susvimo) is an innovative drug delivery system that includes a refillable ocular implant for the continuous delivery of a customized formulation of ranibizumab into the vitreous.[11] The PDS implant can be refilled via clinic-based refill-exchange procedures.[12] The PDS 100 mg/mL with fixed refill-exchanges every 24 weeks (PDS q24w) was recently approved by the U.S. Food and Drug Administration (FDA) for the treatment of nAMD in patients who have previously responded to ≥2 anti-VEGF intravitreal injections.[13] The FDA issued a boxed warning for the PDS because it has been associated with a 3-fold higher rate of endophthalmitis compared with monthly intravitreal injections of ranibizumab.[13] The PDS clinical trial program in nAMD, including the Phase 2 LADDER trial (NCT02510794)[11,14] and Phase 3 Archway trial (NCT03677934),[12] demonstrated that treatment with PDS 100 mg/mL resulted in vision and anatomic outcomes comparable with those of monthly intravitreal ranibizumab 0.5-mg injections. Adverse events related to the PDS procedures were well understood, manageable by trial investigators, and overall did not lead to irreversible vision loss. The long-term safety and efficacy of PDS q24w for nAMD is being evaluated in the Portal extension trial (NCT03683251).[15]

Methods

Archway was a Phase 3, randomized, active treatment–controlled trial for the treatment of nAMD, conducted at 78 study locations in the United States.[12] Patients with nAMD who were previously treated with and responsive to anti-VEGF treatment were randomized 3:2 to PDS q24w (n = 248) or intravitreal ranibizumab 0.5-mg injections every 4 weeks (monthly ranibizumab; n = 167). Patients had received a mean of 5 anti-VEGF injections before randomization. Archway evaluated the safety and efficacy of PDS q24w for 2 years (96 weeks, 4 full treatment intervals). Archway evaluated noninferiority (NI) and equivalence of PDS q24w vs. monthly ranibizumab on the primary endpoint of BCVA (Early Treatment Diabetic Retinopathy Study letters) change from baseline, averaged over Weeks 36 and 40 (NI margin, –4.5 letters; equivalence margin, ± 4.5 letters) and secondary endpoints of BCVA change from baseline averaged over Weeks 60 and 64, and Weeks 88 and 92 (NI margin, –3.9 letters). Patients who completed the study at Week 96 were eligible to enter the open-label extension study, Portal.

Portal is an ongoing, multicenter, open-label extension study enrolling patients who completed the LADDER or Archway trials or who will have participated in the Velodrome trial (NCT04657289).[16] In Portal, patients who were treated with the PDS in LADDER or Archway receive PDS q24w starting on Study Day 1. Patients who received monthly ranibizumab in LADDER or Archway were offered the opportunity to undergo PDS implant insertion and initial fill with ranibizumab 100 mg/mL at Day 1 and then receive PDS refill-exchanges q24w.

Results

In Archway, PDS q24w was noninferior to monthly ranibizumab at Weeks 60 and 64, and Weeks 88 and 92, with differences in adjusted mean (95% CI) BCVA change from baseline of +0.4 (–1.4, +2.1) and –0.6 (–2.5, +1.3) letters between arms, respectively. Adjusted mean BCVA changes from baseline averaged over Weeks 60 and 64, and Weeks 88 and 92, respectively, were –0.4 and –1.1 letters in the PDS q24w arm and –0.8 and –0.5 letters in the monthly ranibizumab arm. Adjusted mean center point thickness change from baseline was generally similar between arms through Week 96. During each of the 4 PDS q24w treatment intervals, 98.4%, 94.6%, 94.8%, and 94.7% of PDS patients assessed did not receive supplemental ranibizumab treatment. The PDS ocular safety profile was generally consistent with the primary analysis.

Results from the Archway cohorts of Portal, with a follow-up time of 3 years since enrollment in the Archway trial, will be presented.

Discussion

The 2-year Archway results support the conclusions from the primary analysis, showing maintenance of efficacy over the entire trial. PDS q24w resulted in vision outcomes that were noninferior to monthly ranibizumab at multiple points of the trial. Through each of the 4 PDS q24w treatment intervals, ~95% of PDS patients assessed did not receive supplemental treatment. Adverse events were generally manageable, with learnings continually implemented to optimize patient outcomes. The 3-year follow-up of the PDS patients implanted in Archway will be informative of long-term outcomes with PDS q24w. Additionally, information about outcomes of patients from the monthly ranibizumab arm of Archway who received PDS implants in Portal will be informative on outcomes of patients who were treated with anti-VEGF injections for ≥2 years before receiving the PDS implant.

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; Vision Loss Expert Group of the Global Burden of Disease Study. 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. Lucentis [package insert]. South San Francisco, CA: Genentech, Inc.; 2018.
5. Eylea [package insert]. Tarrytown, NY: Regeneron Pharmaceuticals, Inc.; 2019.
6. 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.
7. Gohil R, Crosby-Nwaobi R, Forbes A, Burton B, Hykin P, Sivaprasad S. Caregiver burden in patients receiving ranibizumab therapy for neovascular age related macular degeneration. *PLoS One*. 2015; 10(6):e0129361.
8. 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.
9. Varano M, Eter N, Winyard S, Wittrup-Jensen KU, Navarro R, Heraghty J. Current barriers to treatment for wet age-related macular degeneration (wAMD): findings from the wAMD patient and caregiver survey. *Clin Ophthalmol*. 2015; 9:2243-2250.
10. Vukicevic M, Heraghty J, Cummins R, Gopinath B, Mitchell P. Caregiver perceptions about the impact of caring for patients with wet age-related macular degeneration. *Eye (Lond)*. 2016; 30(3):413-421.
11. 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.
12. Holekamp NM, Campochiaro PA, Chang MA, et al; Archway Investigators. Archway randomized Phase 3 trial of the Port Delivery System with ranibizumab for neovascular age-related macular degeneration. *Ophthalmology* 2022; 129(3):295-307.
13. Susvimo [prescribing information]. South San Francisco: Genentech, Inc. ; 2022.
14. Khanani AM, Callanan D, Dreyer R, et al; Ladder Investigators. 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*. 2021; 5(8):775-787.
15. ClinicalTrials.gov. Extension study for the Port Delivery System With Ranibizumab (Portal) (Portal) [NCT03683251]. https://clinicaltrials.gov/ct2/show/NCT03683251. Last update posted May 10, 2022.
16. ClinicalTrials.gov. A study of the efficacy, safety, and pharmacokinetics of a 36-week refill regimen for the port delivery system with ranibizumab in patients with neovascular age-related macular degeneration (Velodrome) [NCT04657289]. https://clinicaltrials.gov/ct2/show/NCT04657289. Last update posted June 9, 2022.

Biosimilar Trials for Retinal Diseases: Recent Clinically Relevant Safety and Efficacy Results

Susan B Bressler MD

In 2009 the Biologics Price Competition and Innovation Act (BPCI) created an abbreviated approval pathway for biosimilar products as a way to provide the public with greater access to biological products that are shown to be biosimilar to or interchangeable with an FDA-licensed reference product. Biologic drugs are genetically engineered proteins that are derived from human genes and expressed in eukaryotic or prokaryotic cell lines. These large and complex agents each have their own unique manufacturing process, with acceptable in-product variation. Other than the gene sequence, little about the manufacture of originator biologics is in the public domain.

Biosimilars differ from generic drugs. A generic drug is an identical copy of a small molecule drug that uses the same chemical formula and synthesis as the originator. Its development takes about 2 years with costs of about 2 million USD. A biosimilar is not an exact copy of the originator biologic; rather, it may have minor differences in clinically inactive components, particularly since it is made in living cells and the manufacturing process is dependent on reverse engineering. Typical development spans 8-10 years, with costs of up to 200 million USD. However, this is 5-7 years shorter and 1-2 billion USD less expensive than the development path for the originator biologic.

Originator biologics require intensive investment (time/money) in clinical studies (Phase 1, 2, and 3). At least 2 Phase 3 clinical trials are required in each disease indication the developer seeks approval for in order to establish efficacy and safety vs. the standard of care in the disease-specific population. As biosimilar agents are required to be "highly similar" to existing innovator biologics, the burden of proof lies in establishing physiochemical properties, pharmacokinetics, pharmacodynamics, immunogenicity, safety, and efficacy comparable to those of the originator product. The greatest investment is in design specification of the product and demonstrating the analytical similarity of the product to the originator. Validation of similarity is sought in a clinical trial in a sensitive patient population using a sensitive endpoint, choosing among the disease indications for which the originator has regulatory approval. The single clinical trial aims to confirm noninferior clinical outcomes with safety signals similar to those of the originator biologic.

Regulatory agencies evaluating a proposed biosimilar take into account the analytical assays, preclinical toxicity, pharmacokinetics, pharmacodynamics, immunogenicity, clinical trial results, and manufacturing process to control in-product variation. The approval application may request "extrapolation" to the other disease indications for which the originator product has approval despite the absence of clinical study of the proposed biosimilar in these other disease indications. If successful switch studies have been performed in which participants have repeatedly been switched from originator to biosimilar and back again with comparison to a group consistently receiving the originator, the application may request an interchangeability designation. Interchangeability permits substitution of the biosimilar for the originator at the time prescriptions are filled, depending on individual state regulations. Biosimilar agents typically launch in the United States with initial list prices 15% to 35% lower than comparative list prices for the reference product.

Phase 3 studies of 2 FDA-approved ranibizumab biosimilar agents in neovascular AMD, Byooviz (ranibizumab-nuna) and Cimerli (ranibizumab-eqrn), and 1 proposed aflibercept biosimilar in DME, MYL-1701P, will be used to illustrate these concepts.

Development of a Disease Activity Scale for Neovascular AMD

Usha Chakravarthy MBBS PhD and Beatriz Garcia Armendariz PhD

The pathophysiology of neovascular AMD (nAMD) is largely driven by the overexpression of VEGF resulting in alteration of the homeostasis of the retina/choroidal interface. This is manifested by the following:

- Neovascularization
- Leakage
- Hemorrhage
- Fluid in different compartments
  - Subretinal fluid
  - Intraretinal fluid
  - Sub–retinal pigment epithelial (sub-RPE) fluid
- RPE detachment
- Retinal layers disorganization
- Atrophy of the RPE/photoreceptors
- Choroidal thinning

There is considerable heterogeneity at a patient level in how the disease manifests, giving rise to variable outcomes on treatment with anti-VEGF agents.

Central subfield thickness (CST) is the most commonly used proxy as a measure of disease severity for progression and to assess response to therapy for retreatment decisions. It is easily extracted from the outputs from most OCT devices. However, it has a poor correlation with vision and has obvious limitations in respect to associations with disease severity, as it relies heavily on appropriate segmentation and the exudative manifestations have differential effects on function based on their compartmental localization. For example, intraretinal fluid has a stronger adverse effect on function than subretinal fluid, and hyperreflective material in the subretinal space is also more damaging to function compared to sub-RPE material.

We developed a scale-based scoring system to describe disease activity at presentation and during follow-up by using structured, objective feature–based classification, that is, a semiquantitative graded categorical approach (5 categories: none, minimal, mild, moderate, and severe) for intraretinal fluid, subretinal hyperreflective material, subretinal fluid, and RPE detachment. For each level, exemplar images were extracted from a clinical trial dataset. Graders assessed disease activity severity at the treatment-naïve stage and at a single visit 1 month later.

The scale was found to be reproducible, with good agreement between graders.

This scale was cross-validated against BCVA and CST. The cross-sectional and longitudinal analyses revealed improved correlations between the disease activity scale and BCVA (r^2 0.64) compared to CST and BCVA (r^2 0.35). Additional analyses are ongoing to determine volume cutoffs for each of the individual fluid compartments.

In summary, validation showed that the scale worked well; it was easy to use and pragmatic, and it was linked to severity within each retinal tissue compartment, namely, intraretinal, subretinal, and sub-RPE.

Long-term Effect of the Anti-VEGF Treatment: A 12-Year Experience

Giovanni Staurenghi MD

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Retinal Microvascular Abnormalities Masquerading as Neovascular AMD

K Bailey Freund MD, Diogo Cabral MD, Prithvi Ramtohul MD, and Ana Fradinh MsCo

Traditional classification schemes for AMD have often used the terms "wet" vs. "dry," "exudative" vs. "nonexudative," and "neovascular" vs. "non-neovascular" interchangeably to distinguish eyes with macular neovascularization (MNV) from those without MNV. While the onset of MNV in AMD eyes is frequently defined by the identification of exudation through multimodal imaging, advances in imaging technology have improved sensitivity for detecting MNV prior to the onset of exudation. Recently, the term "nonexudative MNV" was introduced to describe this clinical presentation. While subretinal fluid in the absence of MNV may occur with acquired vitelliform lesions, in association with soft drusen, and overlying or at the margin of drusenoid pigment epithelial detachments, recently an exudative form of non-neovascular AMD was described in which fluid producing intraretinal edema originates from native retinal vessels within the deep vascular complex.

Hartnett et al were the first to recognize that in eyes with advanced AMD, intraretinal MNV could be identified overlying pigment epithelial detachments. They termed this finding an "outer retinal angiomatous lesion." In subsequent years, clinicopathologic correlation studies and advances in high-resolution multimodal imaging enabled a better characterization of this entity, which was renamed "type 3 MNV" to reflect its anatomic location within the retina. The current understanding of type 3 MNV is that it is a downgrowth of new vessels originating from the deep vascular complex and extending toward the level of the retinal pigment epithelium (RPE)/basal laminar deposits. Translational evidence supports the idea that neovessels develop in intermediate AMD secondary to imbalanced levels of growth and inhibitor factors for angiogenesis, where high levels of vascular endothelial growth factor (VEGF) play a major role. This hypothesis has been corroborated by clinical observation of non-neovascular exudation and type 3 MNV lesions originating in areas with substantial photoreceptor, RPE layer disruption, and intraretinal RPE migration. Non-neovascular microvascular anomalies associated with increased VEGF expression include capillary dilations and telangiectasia and have been reported in eyes with neovascular AMD and non-neovascular AMD.

Previous studies have demonstrated that registration and volume averaging of multiple OCT angiography acquisitions can compensate for motion artifacts and reduce speckle noises. While early algorithms were memory intensive and time consuming, recent advances have enabled more efficient processing of multiple swept source OCT angiography acquisitions with enhanced image quality. Likewise, high-resolution OCT, a recent refinement in spectral domain OCT, increases axial optical resolution to 3 µm, enabling more precise identification of retinal structures. In this study, high-resolution OCT and averaged swept source OCT angiography were used to explore the 3-dimensional structure and vascular connectivity of deep capillary plexus microvascular changes in patients with intermediate AMD. The goal was to distinguish non-neovascular microvascular anomalies producing intraretinal exudation from type 3 MNV. The specific features of these non-neovascular lesions may merit a descriptive terminology, and "deep retinal age-related macular anomalies" (DRAMA) was proposed to describe them.

Selected Readings

1. Hartnett ME, Weiter JJ, Garsd A, Jalkh AE. Classification of retinal pigment epithelial detachments associated with drusen. *Graefes Arch Clin Exp Ophthalmol*. 1992; 230(1):11-19.
2. Querques G, Souied EH, Freund KB. How has high-resolution multimodal imaging refined our understanding of the vasogenic process in type 3 neovascularization? [Editorial] *Retina* 2015; 35(40:603-613.
3. Tan ACS, Dansingani KK, Yannuzzi LA, et al. Type 3 neovascularization imaged with cross-sectional and en face optical coherence tomography angiography. *Retina* 2017; 37:234-246.
4. Sacconi R, Freund KB, Yannuzzi LA, et al. The expanded spectrum of perifoveal exudative vascular anomalous complex. *Am J Ophthalmol*. 2017; 184:137-146.
5. Sacconi R, Sarraf D, Garrity S, et al. Nascent type 3 neovascularization in age-related macular degeneration. *Ophthalmol Retina*. 2018; 2:1097-11061.
6. Sacconi R, Borrelli E, Sadda SV, et al. Nonexudative perifoveal vascular anomalous complex: the subclinical stage of perifoveal exudative vascular anomalous complex? *Am J Ophthalmol*. 2020; 218:59-67.
7. Bacci T, Essilfie JO, Leong BCS, Freund KB. Exudative non-neovascular age-related macular degeneration. *Graefes Arch Clin Exp Ophthalmol*. 2021; 259:1123-1134.
8. Hilely A, Au A, Freund KB, et al. Non-neovascular age-related macular degeneration with subretinal fluid. *Br J Ophthalmol*. 2021; 105:1415-1420.
9. Cao D, Leong B, Messinger JD, et al. Hyperreflective foci, optical coherence tomography progression indicators in age-related macular degeneration, include transdifferentiated retinal pigment epithelium. *Invest Ophthalmol Vis Sci*. 2021;62(10):34.
10. Berlin A, Cabral D, Chen L, et al. Correlation of optical coherence tomography angiography of type 3 macular neovascularization with corresponding histology. *JAMA Ophthalmol*. Epub ahead of print 2022 Apr 21. doi: 10.1001/jamaophthalmol.2022.0890.

Neovascular AMD Panel Discussion

Panel Moderator: Andrew A Moshfeghi MD MBA

Panelists: Usha Chakravarthy MBBS PhD, Jay K Chhablani MBBS, Christina J Flaxel MD, James C Folk MD, Timothy W Olsen MD, and Dimitra Skondra MD

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Uveitic Macular Edema

Annotated Bibliography

Douglas A Jabs MD MBA

1. Tomkins-Netzer O, Lightman S, Drye L, et al.; 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. *Despite treatment, uveitic macular edema is persistent in 40% of eyes at 2 years of therapy. Even with control of the inflammation by systemic therapy, 62% of eyes with uveitic macular edema needed 1-2 adjunctive regional corticosteroid injections in the first 2 years.*
2. Tomkins-Netzer O, Lightman S, Burke AE, et al. 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, whereas recurrence of macular edema was associated with a decline in macular edema.*
3. Thorne JE, Sugar EA, Holbrook JT, et al. 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 intraocular pressure to ≥30 mm Hg was infrequent (≤6%) and similar among the 3 groups.*
4. Lehpamer B, Moshier E, Pahk P, et al. 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.*

Management of Acute Retinal Necrosis in 2022

Thomas A Albini MD

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Uveitis Panel Discussion

Panel Moderator: Sunil K Srivastava MD

Panelists: Nisha Acharya MD, Debra A Goldstein MD, Lucia Sobrin MD, and Edmund Tsui MD

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Is the Retinal Far Periphery Important for Diabetic Retinopathy? Lessons from DRCR Retina Network Protocol AA

Jennifer K Sun MD and the DRCR Retina Network

I. Background

A. The Early Treatment Diabetic Retinopathy Study Diabetic Retinopathy Severity Scale (ETDRS DRSS), which is used to evaluate 7 defined retinal fields on stereoscopic color fundus photographs, is the established method for grading diabetic retinopathy (DR).[1]

1. These fields are focused primarily on the posterior pole and capture only 30%-35% of the retinal surface.

2. Baseline ETDRS DRSS level has been shown to be highly predictive of future risk of DR worsening.[2,3]

B. Ultrawide-field (UWF) imaging can capture up to 82% of the retina in a single image,[4] thereby allowing greater visualization of the retinal far periphery than with ETDRS protocol photographs and improved ability to identify peripheral DR lesions outside the standard ETDRS 7 fields.

C. Primary objective: To determine whether the presence of predominantly peripheral lesions (PPL) identified on UWF imaging is associated with increased disease worsening beyond the risk associated with baseline ETDRS DR severity score (DRSS)

II. Methods

A. Study design: a prospective multicenter longitudinal observational study conducted by the DRCR Retina Network

B. Major eligibility criteria

1. Participants with type 1 or 2 diabetes, 18 years or older

2. At least 1 eye with nonproliferative DR (NPDR) confirmed on ETDRS modified 7-field grading

a. No history of panretinal (scatter) photocoagulation (PRP)

b. No history of intravitreal treatment over the prior 12 months

c. PRP or intravitreal treatment not anticipated within 6 months of enrollment

C. Treatment: Initiation of treatment for DR or diabetic macular edema (DME) was at investigator discretion.

D. Visit schedule

1. Follow-up visits occurred annually for 4 years

2. At each visit, images were acquired with the Optos 200Tx or Optos California (Optos PLC; Dunfermline, Scotland, UK) after pupillary dilation.

a. Acquisition of ETDRS 7-field photographs was discontinued after baseline.

b. UWF fluorescein angiography (FA) was required at baseline and at 1- and 4-year visits.

E. PPL: defined as DR lesions (hemorrhages and/or microaneurysms [H/Ma], intraretinal microvascular abnormalities [IRMA], venous beading [VB], and new vessels elsewhere [NVE]) with a greater extent outside vs. inside the standard ETDRS 7 fields

III. Results

A. Analysis cohort: 544 study eyes (367 participants) from 37 U.S. and Canadian sites

B. 4-year visit completion rate: 77% excluding deaths

C. Baseline characteristics

1. Median age: 62; 50% females; 68% non-Hispanic white

2. Median visual acuity letter score: 86 letters (~Snellen equivalent 20/20)

3. PPL present in 41% of eyes on UWF-color (color-PPL) and 46% of eyes on UWF-FA (FA-PPL)

a. 25% had PPL present on both.

b. 20% had FA-PPL only.

c. 16% had color-PPL only.

d. 39% had PPL absent on both.

D. Treatment initiation over 4 years

1. 18% of eyes initiated treatment for DR or DME.

a. 11% received treatment for DR.

b. 14% received treatment for DME.

2. 1% of eyes received treatment with anti-VEGF, steroid, or vitrectomy for conditions other than DR or DME.

E. Primary outcome: Cumulative proportion of ≥2 steps worsening of DRSS assessed within the ETDRS fields from the UWF-color images or receipt of DR treatment over 4 years
   1. Overall: 40%
   2. By baseline DRSS on UWF-color masked images
      a. 45% with mild NPDR
      b. 40% with moderate NPDR
      c. 26% with moderately severe NPDR
      d. 43% with severe or very severe NPDR
   3. By baseline color-PPL (present vs. absent): 38% vs. 43% (adjusted HR = 0.78; 95% CI, 0.57-1.08; *P* = .13)
   4. By baseline FA-PPL (present vs. absent): 50% vs. 31% (adjusted HR =1.72; 95% CI, 1.25-2.36; *P* < .001)

F. Secondary outcomes
   1. Development of PDR or receipt of DR treatment over 4 years
      a. By baseline color-PPL (present vs. absent): 17% vs. 26% (adjusted HR = 0.90; 95% CI, 0.57-1.44; *P* = .67)
      b. By baseline FA-PPL (present vs. absent): 24% vs. 20% (adjusted HR = 1.60; 95% CI, 1.05-2.45; *P* = .03)
   2. Development of vitreous hemorrhage or receipt of DR treatment over 4 years
      a. By baseline color-PPL (present vs. absent): 10% vs. 12% (adjusted HR = 1.28; 95% CI, 0.67-2.41; *P* = .45)
      b. By baseline FA-PPL (present vs. absent): 12% vs. 11% (adjusted HR = 1.43; 95% CI, 0.79-2.59; *P* = .24)

IV. Conclusions

A. Although no association was identified with color-PPL, the presence of FA-PPL was associated with a significantly greater risk of ETDRS DRSS worsening or treatment over 4 years, independent of DR severity level.

B. These results suggest that evaluation of the retinal far periphery is important in best predicting which eyes with NPDR will experience future disease worsening.

C. Peripheral findings on UWF-FA should be incorporated into future DR staging systems, and efforts to develop less invasive and less costly ways to identify FA-PPL and nonperfusion markers, or their surrogates, are warranted.

References

1. Early Treatment Diabetic Retinopathy Study Research Group. Grading diabetic retinopathy from stereoscopic color fundus photographs: an extension of the modified Airlie House classification. ETDRS report number 10. *Ophthalmology* 1991; 98:786-806.
2. Early Treatment Diabetic Retinopathy Study Research Group. Fundus photographic risk factors for progression of diabetic retinopathy. ETDRS report number 12. *Ophthalmology* 1991; 98:823-833.
3. Wilkinson CP, Ferris FL 3rd, Klein RE, et al. Proposed international clinical diabetic retinopathy and diabetic macular edema disease severity scales. *Ophthalmology* 2003; 110(9):1677-1682.
4. Oishi A, Hidaka J, Yoshimura N. Quantification of the image obtained with a wide-field scanning ophthalmoscope. *Invest Ophthalmol Vis Sci*. 2014; 55(4):2424-2431.

Analysis of Anatomic Changes in the Kingfisher Trial: Brolucizumab vs. Aflibercept Treatment in Eyes With Diabetic Macular Edema

Time to Achieve Sustained Dryness in DME Patients in the KESTREL and KITE Studies

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Introduction

- Resolution of retinal fluid is a key therapeutic goal of anti-VEGF treatment in diabetic macular edema (DME).
- KESTREL and KITE were prospective Phase 3 studies investigating the efficacy and safety of brolucizumab in comparison to aflibercept in patients with DME.
- Brolucizumab groups received 5 loading doses every 6 weeks (q6w) followed by 12-week (q12w) dosing, with optional adjustment to every 8 weeks (q8w) if disease activity was identified at predefined assessment visits; aflibercept groups received 5 doses every 4 weeks (q4w) followed by fixed q8w dosing.
- In this post hoc analysis of data from KESTREL and KITE, we assess time to dryness (ie, absence of intraretinal fluid [IRF] and subretinal fluid [SRF]) and time to sustained dryness (ie, absence of IRF and SRF for 2 consecutive visits) in brolucizumab 6 mg-treated patients vs. aflibercept 2 mg-treated patients.

Results

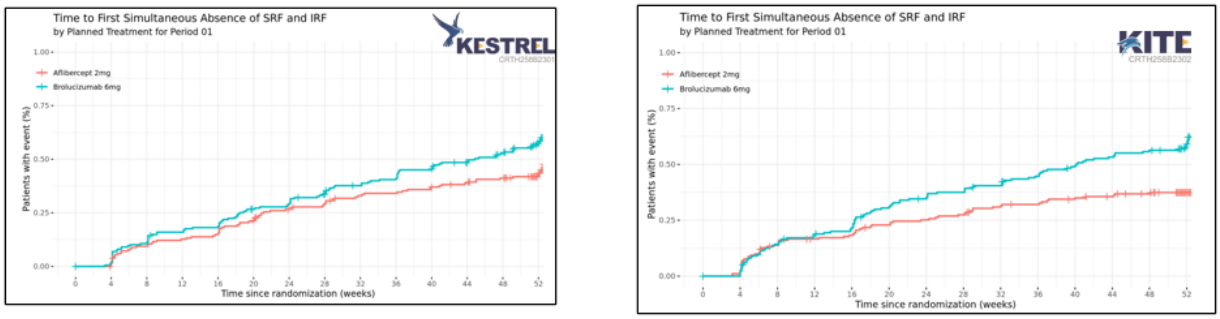

Figure 1. A greater proportion of brolucizumab-treated patients achieved dryness (absence of IRF and SRF) at Weeks 32 and 52 compared to aflibercept-treated patients.

Table 1. Percentiles of Patients Achieving Dryness[a]

	KESTREL		KITE	
	Brolucizumab 6 mg	Aflibercept 2 mg	Brolucizumab 6 mg	Aflibercept 2 mg
Week 32	37.7%	32.9%	40.5%	31.5%
Week 52	56.7%	43.0%	58.6%	37.4%

Abbreviations: IRF, intraretinal fluid; SRF, subretinal fluid.

[a] Based on the absence of IRF and SRF for 2 consecutive visits

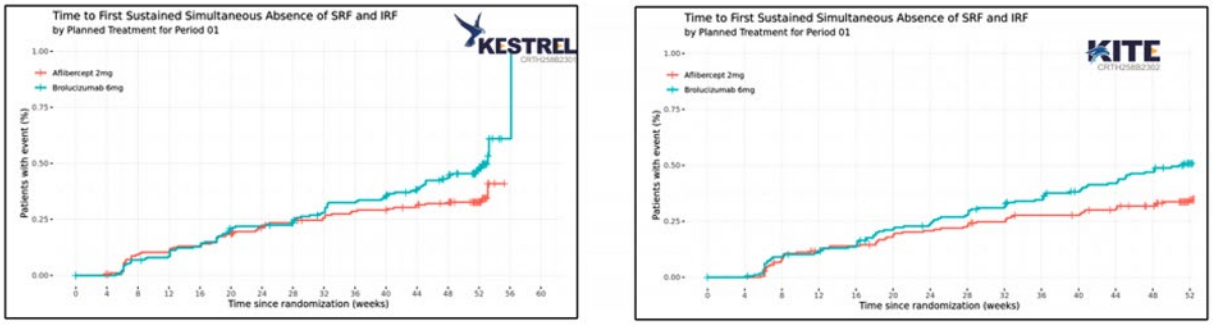

Figure 2. A greater proportion of brolucizumab-treated patients achieved sustained dryness (defined as absence of IRF and SRF for 2 consecutive visits) at Weeks 32 and 52 compared to aflibercept-treated patients.

Table 2. Percentiles of Patients Achieving Sustained Dryness[a]

	KESTREL		KITE	
	Brolucizumab 6 mg	Aflibercept 2 mg	Brolucizumab 6 mg	Aflibercept 2 mg
Week 32	28.0%	25.7%	31.6%	24.8%
Week 52	47.0%	32.7%	50.3%	34.2%

Abbreviations: IRF, intraretinal fluid; SRF, subretinal fluid.

[a] Based on the absence of IRF and SRF for 2 consecutive visits

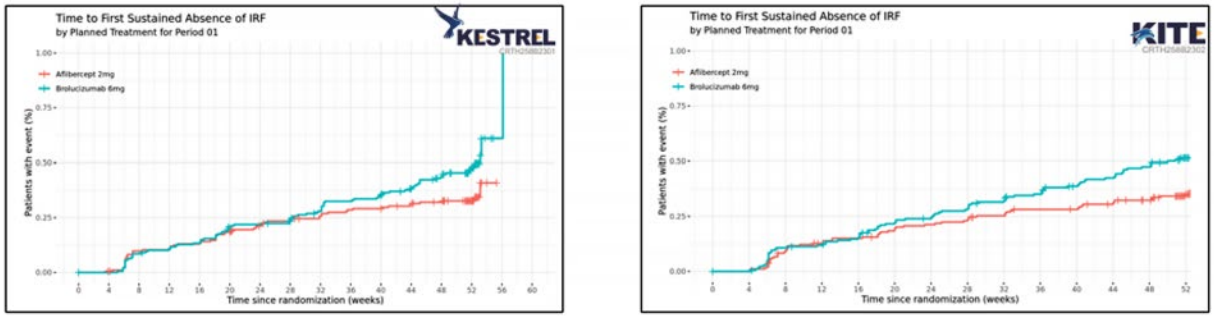

Figure 3. A greater proportion of brolucizumab-treated patients achieved sustained absence of IRF (defined as absence for 2 consecutive visits) at Weeks 32 and 52 compared to aflibercept-treated patients.

Table 3. Percentiles of Patients Achieving Sustained Dryness[a]

	KESTREL		KITE	
	Brolucizumab 6 mg	Aflibercept 2 mg	Brolucizumab 6 mg	Aflibercept 2 mg
Week 32	28.0%	25.7%	32.2%	25.3%
Week 52	47.0%	32.7%	50.9%	34.7%

Abbreviations: IRF, intraretinal fluid; SRF, subretinal fluid.

[a] Based on the absence of IRF and SRF for 2 consecutive visits

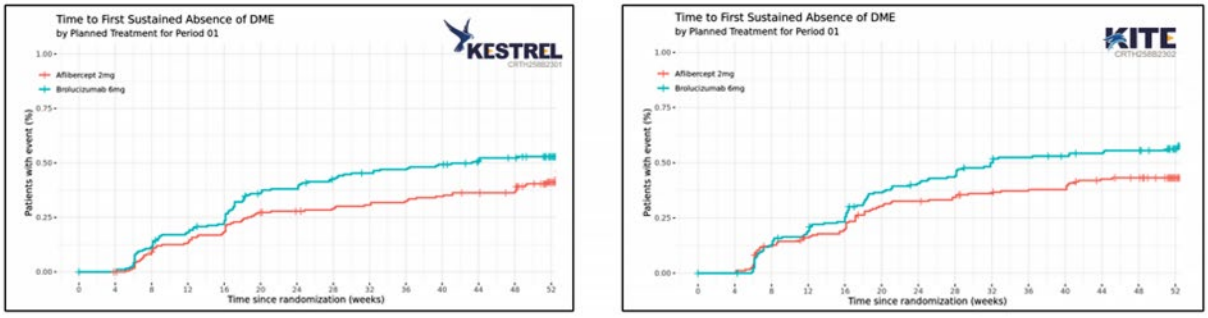

Figure 4. A greater proportion of brolucizumab-treated patients achieved a sustained central subfield foveal thickness (CSFT) <280 µm (defined as CSFT <280 µm for 2 consecutive visits) at Weeks 32 and 52 compared to aflibercept-treated patients.

Table 4. Percentiles of Patients Achieving Sustained Reduction in CSFT[a]

	KESTREL		KITE	
	Brolucizumab 6 mg	Aflibercept 2 mg	Brolucizumab 6 mg	Aflibercept 2 mg
Week 32	45.3%	30.7%	50.0%	36.1%
Week 52	52.9%	40.9%	56.1%	43.2%

Abbreviation: CSFT, central subfield foveal thickness.

[a] Based on a CSFT <280 µm for 2 consecutive visits

Conclusions

- While visual improvements achieved with brolucizumab 6 mg were comparable to aflibercept in KESTREL and KITE, we report important differences in the drying ability of these anti-VEGF therapies.
- A greater percentage of brolucizumab-treated patients achieved dryness and sustained dryness in comparison to aflibercept-treated patients.
- Time to first absence of IRF and SRF was shorter in the brolucizumab 6 mg arm compared with the aflibercept 2 mg arm.
- By Week 52, >50 percent of brolucizumab-treated patients achieved sustained dryness and sustained CSFT <280 µm (KITE only).
- *Additional treatment agnostic analysis on the effect of retinal fluid–free status (absence of IRF, SRF, or sub–retinal pigment epithelium fluid) after the loading phase on visual and anatomic outcomes in DME patients in KITE and KESTREL will also be presented.*
- These findings have important implications for clinicians and patients alike who contend with a high DME treatment and monitoring burden.

Anti-VEGF/anti-Ang2 Year 2 Outcomes for Diabetic Macular Edema and Neovascular AMD

Jennifer I Lim MD

I. Biology of Angiopoietin 1 and 2 and the Tie2 Receptor[1]
   A. Ang1 binds to and activates the Tie2 receptor, resulting in vascular stabilization.
   B. Ang2 binds to Tie2 as a competitive inhibitor of Ang1.
      1. Ang2 levels are increased in pathologic conditions.
      2. This results in destabilization of vessels and potentiates VEGF A effects.

II. Anti-Ang2 Drugs
   A. Faricimab: bispecific antibody (anti-VEGF and anti-Ang2)
   B. Nesvacumab: anti-Ang2
      1. RUBY Phase 2 Trial[2]
      2. No additional visual benefit was seen for low or high dose in combination with aflibercept at Week 12.
   C. Inhibition of vascular endothelial protein tyrosine phosphatase (VE-PTP)
      1. AKB-9778 razuprotafib
      2. TIME 2 studies[3]
   D. Anti-Ang2 drugs in development (BI 836880, RO-634)

III. Clinical Trials of Anti-Ang2 Drugs for Diabetic Macular Edema
   A. Phase 2 BOULEVARD Study[4]
      1. 229 patients (168 treatment-naïve and 61 previously treated with anti-VEGF). In treatment-naïve patients, 6.0-mg faricimab, 1.5-mg faricimab, and 0.3-mg ranibizumab resulted in mean improvements of 13.9, 11.7, and 10.3 Early Treatment Diabetic Retinopathy Study (ETDRS) letters from baseline, respectively.
      2. 6.0-mg faricimab dose resulted in a gain of 3.6 letters over ranibizumab ($P = .03$).
      3. Both faricimab arms resulted in dose-dependent reductions in central subfield thickness (CST), improvements in Diabetic Retinopathy Severity Score (DRSS), and longer time to retreatment during the observation period compared with ranibizumab.
      4. No new or unexpected safety signals
   B. Phase 3 YOSEMITE and RHINE trials[5,6]
      1. Noninferiority trial design (noninferiority margin of 4 ETDRS letters)
         a. 1891 patients in 3 treatment arms
            i. faricimab 6.0 mg every 8 weeks (q8w)
            ii. faricimab 6.0 mg per personalized treatment interval (PTI), or
            iii. aflibercept 2.0 mg q8w up to Week 100
         b. PTI = treat-and-extend regimen based upon change in mean VA and change in CST at dosing visits. Patients were extended, maintained, or reduced (q4w and up to q16w) based on disease activity at active dosing visits.
         c. Primary endpoint = mean change in BCVA at 1 year, averaged over weeks 48, 52, and 56.
      2. Results
         a. Mean change in VA for faricimab q8w or PTI up to 16w were noninferior to aflibercept q8w at both Year 1 and Year 2.
         b. PTI arms for evaluation of durability
            i. q12w or longer
               (a) Year 1: 73.8%/73.1%
               (b) Year 2: 78.1%
            ii. q16w
               (a) Year 1: 52.8%/51%
               (b) Year 2: 60%/64.5%
         c. Secondary endpoints
            i. Comparable proportions of patients in all 3 arms avoided loss of ≥15 letters at Year 2.
            ii. Comparable proportions of patients in all 3 arms gained ≥15 letters at Year 2.
            iii. Greater reductions in CST with faricimab q8w and PTI up to q16w vs. aflibercept q8w at Year 1 were maintained at Year 2.
            iv. Slightly more patients achieved absence of diabetic macular edema at Year 2 with faricimab than aflibercept treatment.

v. More eyes had absence of intraretinal fluid with faricimab than aflibercept at Year 2 and difference was greater than in Year 1.

vi. Absence of subretinal fluid high in all 3 treatment arms by Week 16 and maintained for all 3 arms through Week 100

4. Greater than 2-step improvement in DRSS similar for all 3 arms
   a. aflibercept q8w: 42%/44%
   b. faricimab q8w: 51%/54%
   c. faricimab PTI up to q16w: 43%/44%
5. Safety outcomes
   a. No new safety signals seen
   b. No cases of retinal vasculitis or retinal occlusive vasculitis in any of the 3 arms
   c. Long-term RHONE-X will give 4-year data

IV. Clinical Trials for AMD

Phase 3 Clinical Trials TENEYA and LUCERNE[7,8]: Noninferiority trials comparing faricimab to aflibercept. 1329 patients enrolled into 2 arms: faricimab PTI or aflibercept.

A. Treatment arms
   1. Faricimab 6 mg
      a. Loading doses x4 then q8w, q12w, or q16w through Week 60 depending on disease activity at Week 20
      b. Then PTI beginning after Week 60: intervals extended by 4 weeks (up to q16w), maintained, or reduced by 4 weeks (as low as q8w) based on CST, BCVA, or macular hemorrhage
   2. Aflibercept 2 mg q8w after 3 loading doses

B. Primary endpoint = mean change in BCVA (averaged over weeks 40, 44, 28): was noninferior

C. VA at 2 years: mean change in BCVA remained noninferior VA

D. Durability
   1. >60% of faricimab-treated patients were on q16w and ~80% were on ≥q12w dosing at Year 2.
   2. ~70% of patients who achieved q12w or q16w dosing at Week 60 maintained extended dosing without reducing interval below q12w through Week 108.
   3. ~60% of patients on q8w or q12w dosing at Week 60 were on an increased dosing interval at Week 108.

E. Long-term AVONELLE will give 4-year data.

References

1. 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.
2. Brown DM, Boyer DS, Csaky K, et al; RUBY Investigators. Intravitreal nesvacumab (anti angiopoietin 2) plus aflibercept in diabetic macular edema: Phase 2 RUBY randomized trial. *Retina* 2022; 42(6):1111-1120.
3. Campochiaro PA, Khanani A, Singer M, et al; TIME-2 Study Group. Enhanced benefit in diabetic macular edema from AKB-9778 Tie2 activation combined with vascular endothelial growth factor suppression. *Ophthalmology* 2016; 123(8):1722-1730.
4. 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.
5. Wykoff CC, Abreu F, Adamis AP, et al; YOSEMITE and RHINE Investigators. Efficacy, durability, and safety of intravitreal faricimab with extended dosing up to every 16 weeks in patients with diabetic macular oedema (YOSEMITE and RHINE): two randomised, double-masked, Phase 3 trials. *Lancet* 2022; 399(10326):741-755.
6. Lim JI, Wells JA, Eichenbaum DA, et al. 2-year results from the Phase 3 YOSEMITE and RHINE trials: efficacy, durability, and safety of faricimab in diabetic macular edema. ARVO abstract 2022.
7. Khanani AM, Heier J, Quezada-Ruiz C, et al. Faricimab in neovascular age-related macular degeneration: 1-year efficacy, safety, and durability in the Phase 3 TENAYA and LUCERNE trials. *Invest Ophthalmol Vis Sci*. 2021; 62:428.
8. Khanani A, Demetriades AM, Kotecha A, et al. Faricimab in neovascular age-related macular degeneration: year 2 efficacy, safety, and durability results from the Phase 3 TENAYA and LUCERNE trials. Presented at ASRS 2022; July 14, 2022; New York.

Anti-VEGF Prevention for Severe Nonproliferative Diabetic Retinopathy: A Tale of Two Perspectives

Neil M Bressler MD

NOTES

Real-World Data: What if Diabetic Retinopathy Patients Are Lost to Follow-up?

J Fernando Arevalo MD PhD FACS

Dealing With Patient Loss to Follow-up?

The results of Protocol S raised concerns regarding the effectiveness of anti-VEGF therapy in a real-world setting with inconsistent follow-up. Diabetic patients comprise a vulnerable population that is uniquely prone to loss to follow-up (LTFU).[1-5] A recent retrospective analysis found that even with universal health coverage, patients undergoing anti-VEGF treatment for diabetic retinopathy experienced a significantly higher LTFU rate relative to patients undergoing anti-VEGF treatment for neovascular AMD (29% vs. 3%, respectively; $P < .001$), highlighting the fact that this vulnerability may be independent of treatment method or insurance status.[6] A sampling of Medicare beneficiaries showed that 25% of patients had less than 2 out of 4 fifteen-month intervals with an eye examination over a 5-year follow-up.[1] Among diabetic patients treated for proliferative diabetic retinopathy (PDR), Obeid et al[3] observed the LTFU rate, defined as the rate of an interval greater than 12 months between visits, to be 25.4% over 4 years. Green et al[7] similarly observed a high LTFU rate of 61% in 418 patients over 4 years, although the necessary interval was shortened to 6 months in this study as an effort to include more patients with irreversible damage due to PDR. A larger study that analyzed the LTFU rates in 4423 patients with PDR found a complete LTFU rate of 52% at one year.[8]

Unlike panretinal photocoagulation (PRP), the therapeutic durability of repeated anti-VEGF injections had not yet been established following Protocol S, as the progression of PDR was not measured in patients that experienced LTFU following an initial series of injections. Mirshahi et al[9] reported that a one-time intravitreal bevacizumab (IVB)-augmentation of PRP created a significant but short-lived increase in the PDR regression rate, with 87.5% and 25% of augmented eyes and sham eyes (PRP alone), respectively, showing complete regression of PDR at 6 weeks ($P < .005$). However, the regression rates in the sham and IVB-augmented groups were equal at 16 weeks (25%).[9] The authors concluded that IVB remarkably augmented the short-term response to scatter pan-retinal laser photocoagulation in high-risk PDR, but the effect was short-lived, as many of the eyes experienced rapid recurrence.[9]

In 2019, Obeid et al[10] reported the visual outcomes of 67 eyes that were LTFU for at least 6 months immediately following either anti-VEGF or PRP therapy for PDR. In the anti-VEGF group, the VA at the final visit following LTFU was significantly worse than the last visit prior to LTFU (20/166 vs. 20/54, respectively; $P = .01$).[10] In the PRP group, VA at these 2 time points was not significantly different (20/58 vs. 20/53, respectively; $P = .38$).[10] By the final visit, the anti-VEGF group also experienced more TRD (10 vs. 1; $P = .005$) and iris neovascularization (4 vs. 0; $P = .02$).[10]

Wubben et al[11] investigated 13 eyes of 12 diabetic patients who were LTFU following anti-VEGF therapy for PDR. In these eyes, the median duration of treatment interruption was 12 months. By the time of final follow-up following return, 77% of eyes lost ≥3 lines of VA, with 46% of eyes having a final VA of hand motion or worse.[11] In this case series, LTFU was due to intercurrent illness (31%), noncompliance (31%), and financial issues (15%).[11]

Taken together, the data from these studies[9-11] suggest that the therapeutic durability of intravitreal anti-VEGF injections is low relative to PRP among patients who experience LTFU during PDR treatment. Although Protocol S established the efficacy of anti-VEGF therapy in a randomized clinical trial with frequent, uninterrupted injections, effectiveness is limited by the transient effect of anti-VEGF inhibitors in a diabetic population that is prone to LTFU. The use of PRP should be considered when consistent follow-up is not guaranteed, in order to prevent ongoing progression of PDR and development of associated complications during treatment interruptions.

Real-World Data and PACORES

In 2017, the Pan-American Collaborative Retina Study Group (PACORES) published a retrospective review of the effectiveness of IVB on retinal neovascularization (RN) secondary to PDR with 24 months follow-up.[12] The study included 97 eyes of 81 patients across 5 institutions in Venezuela, Brazil, Argentina, Costa Rica, and Spain. Patients who had previously undergone scatter photocoagulation, prior focal/grid laser photocoagulation, or intravitreal triamcinolone were included if these therapies were performed at least 6 months prior to the study. Subjects received an injection of 1.25 mg of IVB at the initial visit and were reassessed for subsequent injections at each examination. OCT and fluorescein angiography was performed at 1, 3, 6, 12, and 24 months following initial injection. The primary outcome was a change in area of vitreous leakage from RN visualized on fluorescein angiography.

The mean duration of follow-up was 29.6 ± 2 months, and the mean number of IVB injections per eye was 4 ± 2.5. By 24 months, 43.3% of eyes had a BCVA that improved by 2 or more Snellen lines, 50.5% had a BCVA that remained stable, and 6.2% had a BCVA that decreased by 2 or more Snellen lines.[12] At final follow-up, 59.7%, 17.7%, and 22.6% of eyes had complete, partial, and no regression of RN, respectively.[12] Notably, when the data were grouped into eyes that had PRP (61.9% of subjects) at least 6 months before IVB therapy and eyes that were previously untreated (naïve eyes; 38.1%), eyes with prior PRP were more likely to achieve regression of RN. Specifically, 73.3% of eyes with prior PRP experienced complete regression of RN, while 37.9% of naïve eyes experienced complete regression of RN.[12] Of note, in the naïve group, 48.6% of eyes received immediate PRP plus IVB treatment.[12]

For all eyes, BCVA and central macular thickness, as measured by OCT, were significantly improved by 24 months ($P < .0001$).[12] Given that 73.9% of patients with prior PRP had a good response to IVB alone, these findings suggest that IVB therapy alone may be sufficient at controlling PDR and RN in

patients with prior PRP. However, 57.9% of treatment-naïve eyes ultimately progressed to requiring PRP or vitrectomy.[12] Treatment-naïve eyes are at a higher risk for recurrent neovascularization and vision loss if continual follow-up for IVB therapy is not guaranteed.

The limitations of this study include its study design as a retrospective, nonrandomized, and uncontrolled case series. Additionally, the mean number of injections administered in this study, 4 ± 2.5 over 2 years, is lower than those given in Protocol S or the CLARITY study.[13,14] This may limit the study's applicability in clinical situations where more frequent injections are warranted. However, the impact of more frequent injections on patient compliance and follow-up is another factor to consider and one that requires more investigation. The results of the PACORES study, when considered with the data showing high LTFU rates in PDR patients, suggest that a combined treatment paradigm should be considered, with immediate PRP and continued IVB injections for long-term control of PDR and RN.

References

1. Sloan FA, Yashkin AP, Chen Y. Gaps in receipt of regular eye examinations among Medicare beneficiaries diagnosed with diabetes or chronic eye diseases. *Ophthalmology* 2014; 121:2452-2460.
2. Obeid A, Gao X, Ali FS, et al. Loss to follow-up among patients with neovascular age-related macular degeneration who received intravitreal anti–vascular endothelial growth factor injections. *JAMA Ophthalmol*. 2018; 136:1251.
3. Obeid A, Gao X, Ali FS, et al. Loss to follow-up in patients with proliferative diabetic retinopathy after panretinal photocoagulation or intravitreal anti-VEGF injections. *Ophthalmology* 2018; 125:1386-1392.
4. Schoenfeld ER, Greene JM, Wu SY, Leske MC. Patterns of adherence to diabetes vision care guidelines. *Ophthalmology* 2001; 108:563-571.
5. Paz SH, Varma R, Klein R, et al. Noncompliance with vision care guidelines in Latinos with type 2 diabetes mellitus. *Ophthalmology* 2006; 113:1372-1377.
6. Angermann R, Rauchegger T, Nowosielski Y, et al. Treatment compliance and adherence among patients with diabetic retinopathy and age-related macular degeneration treated by anti-vascular endothelial growth factor under universal health coverage. *Graefes Arch Clin Exp Ophthalmol*. 2019; 257:2119-2125.
7. Green M, Tien T, Ness S. Predictors of lost to follow-up in patients being treated for proliferative diabetic retinopathy. *Am J Ophthalmol*. 2020; 216:18-27.
8. Suresh R, Yu HJ, Thoveson A, et al. Loss to follow-up among patients with proliferative diabetic retinopathy in clinical practice. *Am J Ophthalmol*. 2020; 215:66-71.
9. Mirshahi A, Roohipoor R, Lashay A, et al. Bevacizumab-augmented retinal laser photocoagulation in proliferative diabetic retinopathy: a randomized double-masked clinical trial. *Eur J Ophthalmol*. 2008; 18:263-269.
10. Obeid A, Su D, Patel SN, et al. Outcomes of eyes lost to follow-up with proliferative diabetic retinopathy that received panretinal photocoagulation versus intravitreal anti–vascular endothelial growth factor. *Ophthalmology* 2019; 126:407-413.
11. Wubben TJ, Johnson MW, Sohn EH, et al. Anti–vascular endothelial growth factor therapy for diabetic retinopathy: consequences of inadvertent treatment interruptions. *Am J Ophthalmol*. 2019; 204:13-18.
12. Arevalo JF, Lasave AF, Wu L, et al. Intravitreal bevacizumab for proliferative diabetic retinopathy: results from the Pan-American Collaborative Retina Study Group (PACORES) at 24 months of follow-up. *Retina* 2017; 37:334-343.
13. Writing Committee for the Diabetic Retinopathy Clinical Research Network; Gross JG, Glassman AR, Jampol LM, et al. Panretinal photocoagulation vs intravitreous ranibizumab for proliferative diabetic retinopathy: a randomized clinical trial. *JAMA* 2015; 314:2137.
14. 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; 389:2193-2203.
15. Arevalo JF, Beatson B; Pan-American Collaborative Retina Study Group (PACORES). Lessons learned from PACORES in proliferative diabetic retinopathy management, data from Latin America and Spain: the Asbury Lecture 2020. *Retina* 2022; 42(1):4-10.

The Role of Inflammation in Diabetic Macular Edema

Baruch D Kuppermann MD PhD

Summary

There is a growing body of evidence supporting a key role for inflammation and associated cytokines in the development of diabetic macular edema (DME). A series of experimental and clinical studies have shown that a variety of inflammatory cytokines exhibit progressive elevation in the development of advancing diabetic retinopathy and macular edema, including MCP-1, IL-6, IL-1β, and others, in addition to VEGF. Clinical studies have shown that steroids are effective in treating macular edema caused by DME. This effect of steroids on the treatment of macular edema appears to be effective both early and late in the development of macular edema, and this effect may be even more pronounced in chronic macular edema. Conversely, there is clinical trial evidence that anti-VEGF therapy seems most effective for the treatment of treatment-naïve or non-chronic macular edema, and less so with chronic disease. Interestingly, there is clinical data showing that treatment of DME with steroids lowers intraocular levels of a wide variety of inflammatory cytokines in addition to VEGF, whereas anti-VEGF injections lower only VEGF levels without any apparent compensatory effect on the inflammatory cytokine cascade. Detailed preclinical and clinical data will be presented supporting the role of inflammation in the development of macular edema, as well as the relative roles of intraocular steroids and anti-VEGF compounds for the treatment of DME.

The Role of Inflammation in DME

The pathophysiology of DME is multifactorial and complex because it involves mechanical and biochemical pathways triggered by prolonged and sustained hyperglycemia leading to alteration of the blood–retinal barrier (BRB) as its hallmark. It is further characterized by pericyte loss and endothelial cell–cell junction breakdown of the BRB.[1] There is a significant body of preclinical and clinical evidence strongly suggesting that DME is an inflammatory disease with multiple cytokines and chemokines involved in its pathogenesis as well as inflammatory-induced involvement of multiple cellular and neuro endocrine units. Hyperglycemia activates the polyol pathway in a reaction catalyzed by aldose reductase using NADPH to reduce excess glucose to sorbitol. In the reaction that follows, some sorbitol is converted to fructose by sorbitol dehydrogenase using NAD+. Most of the sorbitol remains unchanged, thus depleting NADPH. The reduction of NADPH prevents the regeneration of glutathione and other free radical scavengers, increasing oxidative stress on the cell.[2] In addition to these enzymatic pathways, hyperglycemia is also responsible for nonenzymatic glycation of plasma proteins and the basal lamina, which leads to the production of advanced glycation endpoints (AGEs), accumulation of which in the vitreous causes crosslinking of collagen, leading to an abnormally adherent vitreoretinal interface.

Another notable pathway activated by hyperglycemia is the diacylglycerol pathway. This pathway activates protein kinase C (PKC) β isoform, which is found in high concentrations in the retina.[3] Activated PKC-β mediates retinal vascular permeability, through hypoxia transcription factor HIF-1, to upregulate interleukin 6 (IL-6) and subsequently, VEGF signaling pathways, leading to further BRB impairment.[4]

The clinical correlation to the above has been demonstrated in the work of Yoshimura, who showed that inflammation affects the formation and the progression of various vitreoretinal diseases, including DME. In his analysis of 345 vitreous samples from various vitreoretinal diseases, including 92 eyes from DME patients, Yoshimura found that IL-6, IL-8, and MCP-1 were significant inflammatory mediators in DME. Furthermore, he found that various cytokines in the vitreous, including IL-6, IL-8, and MCP-1, increase vascular permeability, leading to the development of DME. He additionally noted in that study that VEGF appears to act independently of the inflammatory cytokines.[5] Dong et al subsequently showed that intraocular VEGF levels are significantly but statically elevated in diabetic eyes regardless of retinopathy levels, whereas inflammatory cytokines such as IL-6, IP-10, and MCP-1 show low levels in mild diabetic retinopathy and progressively higher levels as retinopathy progresses.[6] Clinical trial evidence suggests that there are mechanisms other than VEGF that could be mediating DME. The DRCR.net Protocol I and Protocol T showed that not all patients treated with anti-VEGFs responded adequately to therapy. The early post hoc analysis of the Protocol I groups treated with ranibizumab showed that visual responses to anti-VEGF therapy after the initial 3 monthly ranibizumab injections were highly predictive of long-term outcomes, so that a suboptimal response to anti-VEGF after 3 injections typically remains suboptimal out to 3 years—thus the birth of the "swim lane." Sohn et al showed that DME treated with bevacizumab significantly lowered VEGF levels but no other inflammatory cytokines, whereas eyes treated with triamcinolone exhibited reduced levels of a wide variety of cytokines, including VEGF.[7] Busch and colleagues showed that eyes with a suboptimal anatomical response to 3 monthly injections of anti-VEGF agents responded better by switching to intervention with the dexamethasone implant compared to continuing anti-VEGF therapy.[8]

In conclusion, preclinical and clinical evidence suggests that inflammatory mediators have a significant role in the pathogenesis of DME, and this has significant implications in the management of DME. While anti-VEGF therapy is a mainstay of treatment for DME, it may not be as effective in a subset of clinical cases with high levels of other non-VEGF cytokines, since there is evidence that anti-VEGF therapy primarily reduces only VEGF levels and not other inflammatory cytokines. As such, when a suboptimal response to anti-VEGF is noted (as soon as after 3 monthly intravitreal anti-VEGF injections) in eyes with DME, a switch to intravitreal steroid therapy should be considered rather than continuing anti-VEGF therapy indefinitely.

References

1. Klaassen I, Van Noorden CJ, Schlingemann RO. Molecular basis of the inner blood-retinal barrier and its breakdown in diabetic macular edema and other pathological conditions. *Prog Retin Eye Res*. 2013; 34:19-48.
2. Goldin A, Beckman JA, Schmidt AM, Creager MA. Advanced glycation end products: sparking the development of diabetic vascular injury. *Circulation* 2006; 114:597-605.
3. Das Evcimen N, King GL. The role of protein kinase C activation and the vascular complications of diabetes. *Pharmacol Res*. 2007; 55:498-510.
4. Aiello LP, Bursell SE, Clermont A, et al. Vascular endothelial growth factor-induced retinal permeability is mediated by protein kinase C in vivo and suppressed by an orally effective betaisoform-selective inhibitor. *Diabetes* 1997; 46:1473-1480.
5. Yoshimura T, Sonoda KH, Sugahara M, et al. Comprehensive analysis of inflammatory immune mediators in vitreoretinal diseases. *PLoS One* 2009; 4(12):e8158-8164.
6. Dong N, Xu B, Wang B, Chu L. Study of 27 aqueous humor cytokines in patients with type 2 diabetes with or without retinopathy. *Mol Vis*. 2013; 19:1734-1746.
7. Sohn HJ, Han DH, Kim IT, et al. Changes in aqueous concentrations of various cytokines after intravitreal triamcinolone versus bevacizumab for diabetic macular edema. *Am J Ophthalmol*. 2011; 152:686-694.
8. Busch C, Zur D, Fraser-Bell S, et al; International Retina Group. Shall we stay, or shall we switch? Continued anti-VEGF therapy versus early switch to dexamethasone implant in refractory diabetic macular edema. *Acta Diabetol*. 2018; 55(8):789-796.

Drugs in the Pipeline for Diabetic Eye Disease

David Boyer MD

I. Endpoints
   A. Decrease in macular edema
   B. Decrease in Diabetic Retinopathy Severity Score (DRSS)
   C. Reduction of vision-threatening complications (VTC)
   D. Improvement in ischemia
   E. Longer-acting drugs to improve compliance (cannot have decreased efficacy)

II. First-Line Treatment

   Medical management

III. Drugs in the Pipeline
   A. Anti-VEGF
      1. Brolucizumab
      2. High-dose aflibercept (8 mg)
      3. Port delivery system (PDS)
      4. KSI-301 (Kodiak)
   B. Anti-VEGF plus
      1. OPT-302 VEGFR-2 + VEGFR-3 (VEGF C + D)
   C. Anti-VEGF + Tie2 inhibition
      1. Faricimab (approved)
      2. AKB 9778
   D. Integrin receptor
      1. THR-687 (failed)
      2. ALG-1007
      3. AG-73305
      4. OCU-166
   E. Plasma kallikrein
      1. THR-149
      2. KVD001
      3. RZ-402
      4. Ocutera
   F. Gene therapy
      1. RGX-314
      2. ADVM-022 (failed, not going forward)

Intravitreal Injection the Focus for Drugs in Development

Company	Drug	Target/MOA	Route of Administration	Pre-clinical	Ph1	Ph2	Ph3	Commercial
Regeneron/Bayer	Eylea (aflibercept)	VEGF-A/B; PlGF	Intravitreal (DR & DME)	✓	✓	✓	✓	✓
Roche/Novartis	Lucentis (ranibizumab)	VEGF-A	Intravitreal (DR & DME)	✓	✓	✓	✓	✓
Roche	Ranibizumab PDS	VEGF-A	Surgical/Refill (DME)	-	✓	✓	✓	✓
Roche	Faricimab	VEGF-A x Ang2	Intravitreal (DME)	✓	✓	✓	✓	PDUFA Late Jan 2022
Kodiak	KSI-301	VEGF	Intravitreal (DR & DME)	✓	✓	N/A	○	
~~Kalvista~~	~~KVD001~~	~~Plasma Kallikrein~~	Intravitreal (DME)	✓	✓	✓		
Eli Lilly	LY333531	Protein Kinase C inbitor	Oral (DR)	✓	✓	✓	X 2006	
Ocuphire	**APX3330**	**Ref-1 inhibitor**	**Oral (DR)**	✓	✓	○		
Bayer	BAY1101042	Guanylate Cyclase activator	**Oral (DR)**	✓	✓	○		
Alkahest	AKST4290	CCR3 Eotaxin inhibitor	Oral (DR)	✓	✓	○		
Roche	RG7774	CB2 Receptor	Oral (DR)	✓	✓	○		
Boehringer Ing.	BI 1467335	AOC3	Oral (DR)	✓	✓	X 2021		
Rezolute	RZ402	Plasma Kallikrein	Oral (DME)	✓	✓			
OcuNexus	HCB 1019	Connexin 43 (inflammasome)	Oral (DR)	✓	✓			
OcuTerra	OTT166	Integrin inhibitor	Eyedrop (DR)	✓	✓			

Approved

In Trial

ORAL R_x

Topical

✓*Completed*
○ *Recruiting*
X *Discontinued/Failed study*

Guggenheim report (2020); www.clinicaltrials.gov; Company websites

Figure 1. Key clinical landscape in diabetic retinopathy and diabetic macular edema.

G. Other treatments
   1. TKIs
   2. Endothelin
   3. IL-6
   4. Subthreshold laser
   5. Steroids
   6. Rho kinase inhibitor

Selected Readings

1. Chen X, Khanani AM, Baumal CR. The diabetic eye disease pipeline in 2021. *Retina Today*, November/December 2021.
2. Mansour SE, Browning DJ, Wong K, Flynn HW Jr, Bhavsar AR. The evolving treatment of diabetic retinopathy. *Clin Ophthalmol.* 2020; 14:653-678.
3. Patel P, Shah CP. A peek into the diabetic retinopathy pipeline. *Rev Ophthalmol.* April 15, 2021.
4. Hinkle J, Hsu J. The future looks bright: the therapeutics pipeline for diabetic retinopathy. *Retina Today*. Nov/Dec 2020.
5. DelveInsight. Diabetic retinopathy – pipeline insights. March 2022.

Diabetes Panel Discussion

Panel Moderator: Jennifer K Sun MD

Panelists: Alain Gaudric MD, Dennis M Marcus MD, Purnima S Patel MD, Aleksandra V Rachitskaya MD, and John A Wells III MD

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What's New in the ICROP3 Classification of ROP?

Mary Elizabeth Hartnett MD FACS

I. International Classification of ROP
   A. Original ICROP in 1984
   B. Third edition included input from 34 international pediatric ophthalmologists and retinal specialists who met in person and virtually.
   C. Goals of committee
      1. Address earlier components of classification that were subjective and open to interpretation
      2. Review innovations in ophthalmic imaging that allow identification and comparison of levels of disease severity
      3. Discuss new understanding of pathophysiology with treatments that interfere with VEGF bioactivity
      4. Introduce post-treatment conditions of regression and reactivation
      5. Recognize patterns of ROP in other regions of the world
   D. Classification remains based on zone of involvement, stage of disease severity, plus disease, extent of disease.
   E. ICROP3 focuses on classification and not treatment recommendations.

II. Revised Parameters in ICROP3
   A. Zone secondary to notch (zone described by the lowest zone, but qualified)
   B. Stage
      1. Subclassification of stage 5
         a. 5A: open funnel
         b. 5B: closed funnel and B-scan
         c. 5C: closed funnel and anterior segment involvement
      2. Imaging opportunities important but not necessary for ICROP3. Value of OCT in distinguishing 4A and 4B ROP and schisis and retinal detachment
   C. Plus disease
      1. Spectrum of disease
      2. Level of tortuosity and dilation of retinal vessels determined within zone I
   D. Aggressive ROP (A-ROP)
      1. Includes the previous aggressive posterior ROP (AP-ROP)
      2. Hallmarks
         a. Rapid progression of stage 3 that can be flat and recognized by hemorrhages and plus, without progression through stages
         b. Occurs posteriorly and/or involve peripheral retina also
   E. Regression of type 1 ROP
      1. Lessening of severity of treatment-warranted ROP
         a. Occurs spontaneously or after treatment
         b. Different time courses after anti-VEGF (sooner) than after laser
      2. Reduction in dilation and stage 3
      3. Tortuosity may not resolve completely, especially with heart disease or pulmonary hypertension.
      4. Vascularization of the peripheral avascular retina (VPAR)
         a. Unlike adult vitreoretinal diseases (diabetic retinopathy or remodeling in vein occlusion), VPAR occurs to a degree after anti-VEGF but rarely after laser in ROP.
         b. Involves ordering of endothelial divisions to extend VPAR by regulation of VEGF receptor 2 in endothelial cells
      5. Persistent avascular retina (PAR)
         a. Occurs in some infant retinas with regression spontaneously or after anti-VEGF
         b. Treatment considered to avoid missing reactivation in infants who are difficult to exam in clinic or to reduce risk of later retinal detachment
      6. Progressive stage 4 ROP
         a. More common following laser during times when treatment-warranted ROP for threshold disease
         b. Different features after laser than anti-VEGF
            i. Laser: vitreous haze and condensation over ridge, persistent plus disease
            ii. Elevation of retina at the previous ridge prior to VPAR or reactivated ridge

F. Reactivation

1. Occurs spontaneously or after complete or incomplete regression
2. If stage 3, consider treatment of skip areas with laser or anti-VEGF
3. Reactivation can occur and regress spontaneously; *does not always require treatment*
4. Features
   a. New lines, ridges, dilation and/or tortuosity, extraretinal neovascularization
   b. Zone I can have lacy vessels and hemorrhages; hemorrhages around fronds can suggest flat neovascularization.
   c. Reactivation characterized by adjective, "reactivated"
5. Consensus lacking on when to treat reactivated neovascularization. VPAR can show vascular budding at vascular/avascular junction.

III. Follow-up Care for Preterm Infants (Also Visual Rehabilitation After Retinal Exams)

A. Without ROP through 45 weeks postmenstrual age (PMA)

B. After laser, for progressive stage 4 ROP, then often longer than 50 weeks PMA

C. After anti-VEGF through 65 weeks PMA and laser may be considered for PAR

Selected Readings

1. International Classification of Retinopathy of Prematurity, Third Edition. *Ophthalmology* 2021; 128(10):e51-e68.
2. Hartnett ME, Martiniuk D, Byfield G, Geisen P, Zeng G, Bautch VL. Neutralizing VEGF decreases tortuosity and alters endothelial cell division orientation in arterioles and veins in a rat model of ROP: relevance to plus disease. *Invest Ophthalmol Vis Sci.* 2008; 49(7):3107-3114.
3. Simmons AB, Bretz CA, Wang H, et al. Gene therapy knockdown of VEGFR2 in retinal endothelial cells to treat retinopathy. *Angiogenesis* 2018; 21(4):751-764.
4. Fierson W. Screening examination of premature infants for retinopathy of prematurity. *Pediatrics* 2018; 142(6) :e20183061.

Management of Persistent Avascular Retina and Reactivation in Retinopathy of Prematurity

R V Paul Chan MD

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Three Decades of ROP in an Inner City Hospital

Audina M Berrocal MD

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Pediatric Retina Panel Discussion

Panel Moderator: Yoshihiro Yonekawa MD

Panelists: Kimberly A Drenser MD PhD, G Baker Hubbard MD, Darius M Moshfeghi MD, Aaron Nagiel MD PhD, and Irena Tsui MD

NOTES

Gene Therapy for Atrophic AMD 2022

Allen C Ho MD

Subretinal delivery is currently the only validated approach for delivery of AAV retinal gene therapy.[1] A transvitreal approach to subretinal delivery is currently the standard approach (see Figure 1); however, it requires vitrectomy and a retinotomy. Complications of this technique may include retinal detachment,[2] cataract,[3,4] hemorrhages, IOP changes, endophthalmitis, and loss of vision.

The Orbit Subretinal Delivery System (Orbit SDS)[5] is an innovative proprietary device designed to be a minimally invasive alternative to the transvitreal approach (see Figure 2). Earlier versions of Orbit SDS have been used to successfully deliver investigational cell therapies with an encouraging safety profile.[6]

The FOCUS trial is a Phase 1/2 FOCUS clinical trial evaluating delivery of GT005, an investigational complement factor I (FI)–targeted gene therapy for geographic atrophy (GA), using the Orbit SDS as one of its delivery strategies.

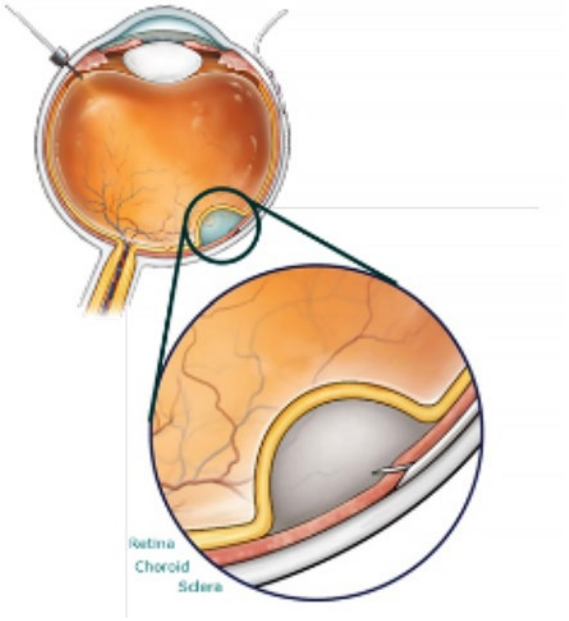

Figure 1. Transvitreal subretinal injection.

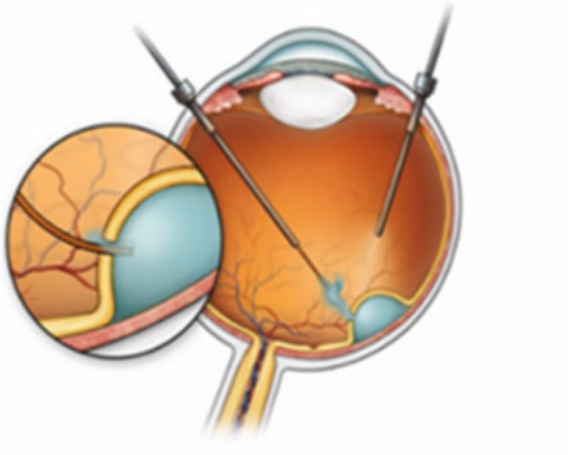

Figure 2. Suprachoroidal canulation with subretinal injection.

Complement inhibition is a validated approach for GA.[7,8]

Overactivation of the complement system leads to inflammation that can damage retinal tissues.[9] Clinical trials have shown that complement inhibition slows growth of GA.[8,10,11]

FI restores balance to an overactive complement system.[12] An important function of FI is to keep the complement system in balance through sequestration of C3, thereby removing it from the alternative pathway amplification loop (see Figure 3).[12]

GT005 is an AAV2-based gene therapy designed to induce expression of FI. After subretinal delivery, GT005 is transduced into the cell and transcribed into mRNA in the nucleus. The FI protein is then translated and secreted out of the cell (see Figure 4).

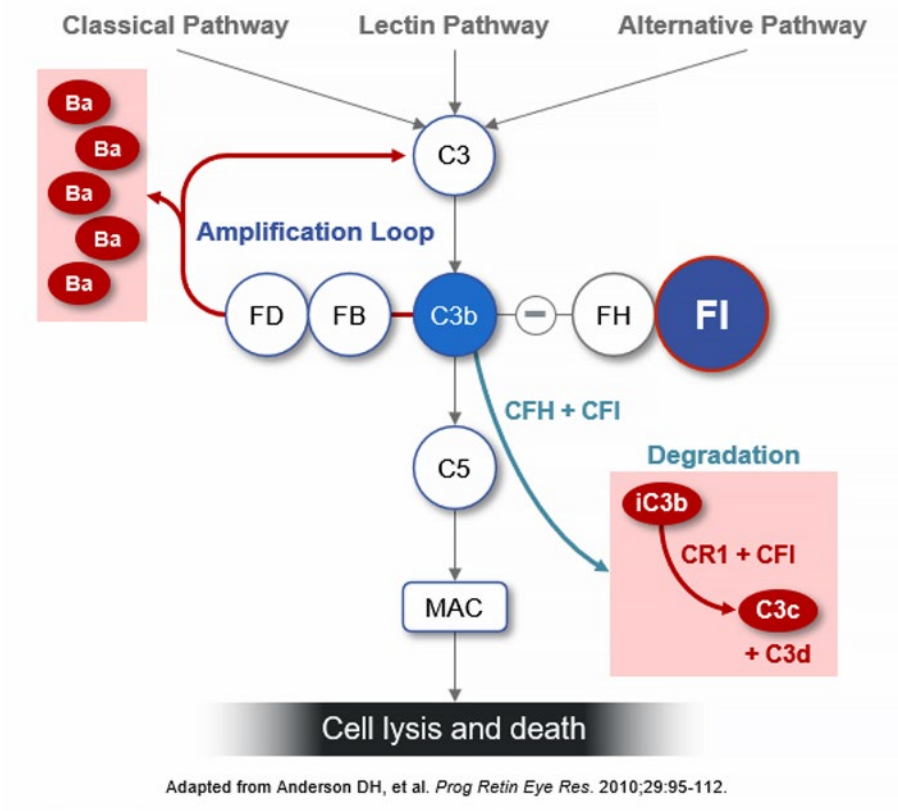

Figure 3. The complement system. Inducing factor I expression leads to continual, sustained decreases in key proteins involved in complement overactivation (C3, Ba, C3b, iC3b).

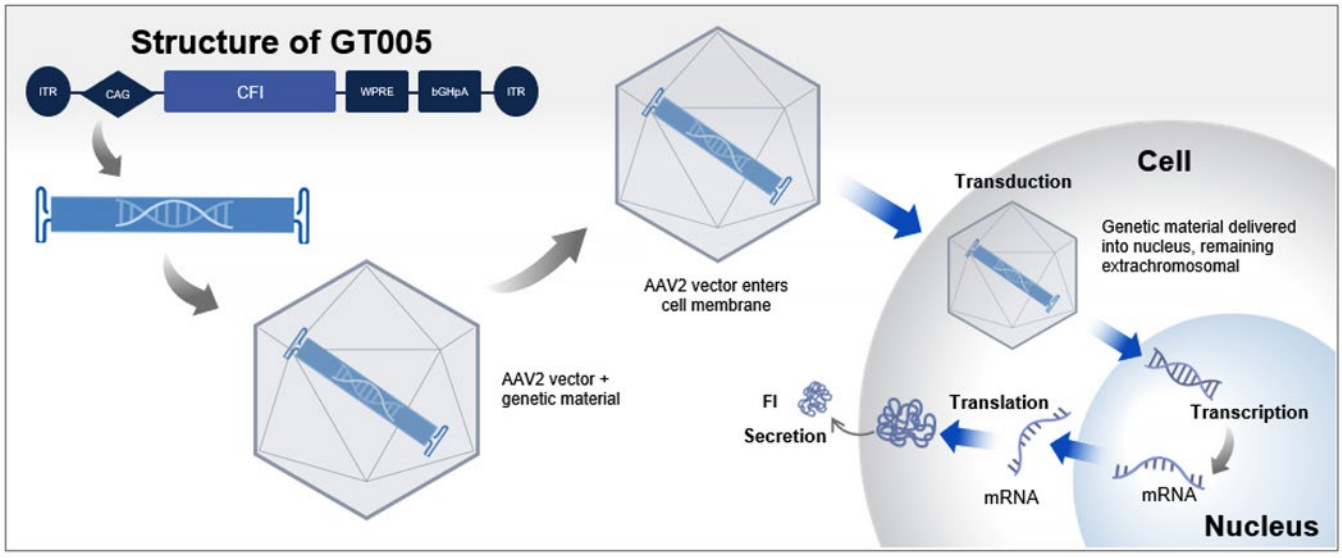

Figure 4. Structure and transduction of GT005.

The FOCUS Trial

The FOCUS trial (NCT03846193) was designed to investigate safety and dose response of GT005, an investigational recombinant adeno-associated viral (AAV2) vector encoding FI, using 2 delivery strategies, transvitreal subretinal injection (TVSI) and suprachoroidal cannulation with subretinal delivery using the Orbit SDS, for treatment of GA secondary to AMD.

The FOCUS trial is an open-label multicenter study consisting of 4 parts (see Figure 5).

Part 1: dose-escalation of GT005 delivered via TVSI (Cohorts 1-3)

Part 2: dose-expansion of GT005 delivered via TVSI (Cohort 4)

Part 3: dose-escalation of GT005 delivered via the Orbit SDS (Cohorts 5 and 6)

Part 4: dose-expansion of GT005 delivered via the Orbit SDS (Cohort 7)

Patients had bilateral GA at baseline and received a single subretinal administration of GT005 in the study eye. Primary endpoint is the incidence of treatment-emergent adverse events (AEs) over 48 weeks, with secondary endpoints including changes in complement protein expression in the vitreous. Cohorts 5 and 6 explored 2 GT005 dose levels (5E10 and 2E11 vector genomes [vg], respectively) delivered via Orbit SDS. Cohort 7 also utilizes Orbit SDS to further explore doses of GT005 that are shown to be safe and tolerated in Cohorts 5 and 6. Enrollment in Cohort 7 is ongoing. Interim data from the Orbit SDS Cohorts 5-7 will be presented.

The Orbit SDS

The Orbit SDS accesses the subretinal space via a suprachoroidal approach. This specially designed system enables cannulation of the suprachoroidal space with a flexible cannula. A microneedle inside the SDS cannula is advanced into the subretinal space to enable targeted dose delivery, without the need for a vitrectomy or a retinotomy (see Figure 6).

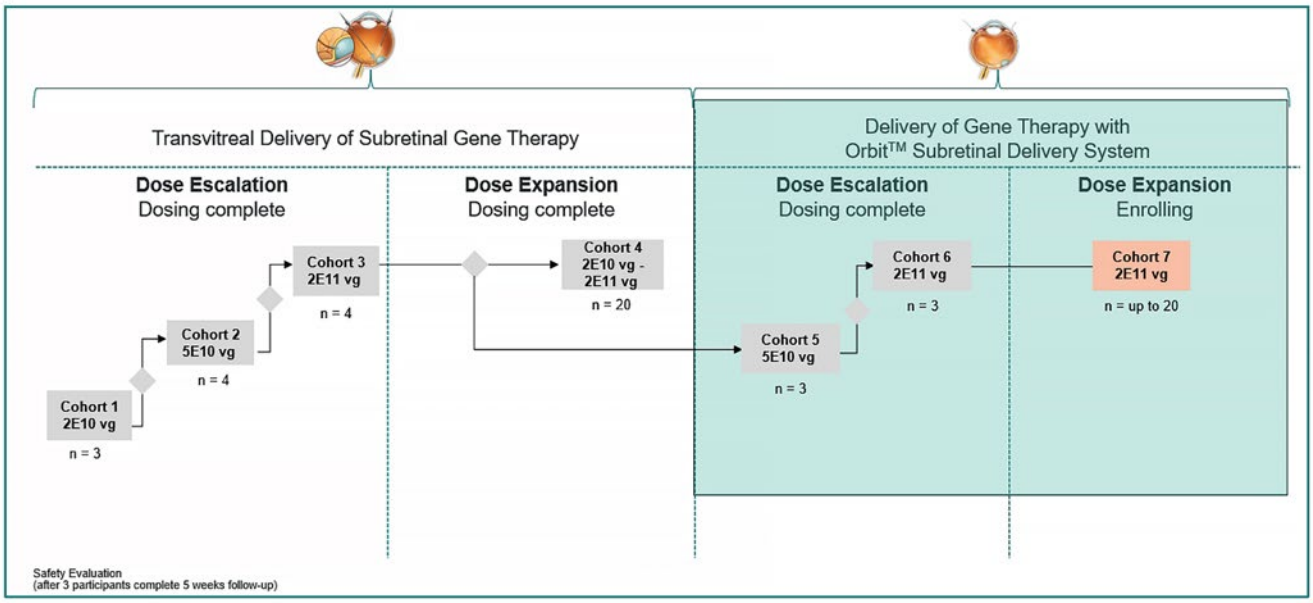

Figure 5. FOCUS trial study design.

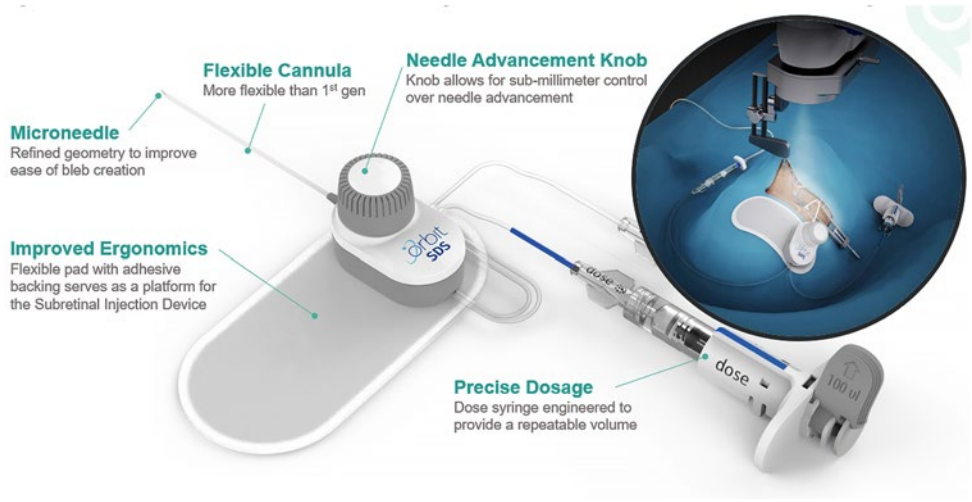

Figure 6. Second-generation Orbit SDS device.

Summary

Gene therapy for atrophic AMD is ongoing in a Phase 1/2 trial using an AAV2 viral vector and a complement FI transgene delivered to the subretinal space via either a transvitreal or a suprachoroidal (Orbit SDS) approach. Complement FI inhibits complement overactivation, and a gene therapy approach may be particularly suited for atrophic AMD.

References

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 randomised, controlled, open-label, Phase 3 trial. *Lancet* 2017; 390(10097):849-860.
2. Stein JD, Zacks DN, Grossman D, et al. Adverse events after pars plana vitrectomy among Medicare beneficiaries. *Arch Ophthalmol*. 2009; 127(12):1656-1663.
3. Cheng L, Azen SP, El-Bradey MH, et al. Duration of vitrectomy and postoperative cataract in the vitrectomy for macular hole study. *Am J Ophthalmol*. 2001; 132:881-887.
4. Holekamp NM, Shui Y-B, Beebe DC. Vitrectomy surgery increases oxygen exposure to the lens: a possible mechanism for nuclear cataract formation. *Am J Ophthalmol*. 2005: 139(2):302-310.
5. *Note*: The Orbit SDS is indicated in the United States for microinjection into the subretinal space. The 510(k) clearance is based upon the use of BSS or BSS PLUS.
6. Riemann CD. Phase 1/2a clinical trial of transplanted allogeneic retinal pigmented epithelium (RPE, OpRegen) cells in advanced dry age-related macular degeneration (AMD): interim result. Presented at Annual Meeting, Retina Society; 2021.
7. 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; 37:819-835.
8. Liao D, Grossi FV, El Mehdi D, et al. Complement C3 inhibitor pegcetacoplan for geographic atrophy secondary to age-related macular degeneration: a randomized Phase 2 trial. *Ophthalmology* 2020; 127:186-195.
9. Lachmann PJ. The amplification loop of the complement pathways. *Adv Immunol*. 2009; 104:115-149.
10. Jaffe GJ, Westby K, Csaky KG, et al. C5 inhibitor avacincaptad pegol for geographic atrophy due to age-related macular degeneration: a randomized pivotal Phase 2/3 trial. *Ophthalmology* 2021; 128:576-586.
11. Wykoff C. Treatment of geographic atrophy secondary to age-related macular degeneration with pegcetacoplan: updates on the randomized Phase 3 DERBY and OAKS trials. Presented at Retina Subspecialty Day, Annual Meeting, American Academy of Ophthalmology; 2021; New Orleans, LA.
12. Lachmann PJ. The story of complement factor I. *Immunobiology* 2019; 224(4):511-517.

Gene Therapy for Neovascular AMD

Peter A Campochiaro MD

I. Ocular Gene Therapy

A. Primary use is for treatment of inherited retinal degenerations

1. Gene augmentation for recessive loss-of-function mutations

a. Leber congenital amaurosis (LCA) from mutations in RPE65[1] has provided proof of concept and is approved.

b. X-linked recessive retinitis pigmentosa (RP) from mutations in RP GTPase regulator protein (RPGR) in clinical trials (NCT04671433, NCT03316560)

2. Gene editing: EDIT-101 for LCA10 in clinical trial (NCT03872479)

B. Sustained expression of therapeutic proteins in common diseases. Gene transfer of antiangiogenic proteins for neovascular AMD (nAMD).

1. Intravitreous injection of an adenoviral vector containing an expression construct for the anti-angiogenic protein, pigment epithelial–derived factor.[2] Several eyes showed improvement providing proof of concept for the strategy and motivating the use of vectors that express for longer durations.

2. Subretinal injection of RetinoStat, a lentiviral vector expressing human endostatin and angiostatin, demonstrated stable, long-term expression of endostatin and angiostatin in the eyes of patients with nAMD, but there were little signs of efficacy.[3] Although endostatin and angiostatin have strong anti-angiogenic activity in mouse models, their activity in humans is uncertain.[4-8]

3. Subretinal injection of an AAV2 vector expressing soluble VEGF receptor 1 (sVEGFR1). Showed some evidence of activity in a small trial[9] but failed to show efficacy in a second trial (NCT01494805).

4. Intravitreous injection of an AAV2 vector expressing modified sVEGFR1 (sFLT01). Mild inflammation and showed some evidence of activity in some patients, but not consistent.[10] In the highest dose cohort (2×10^{10} vg), 5 of 10 patients had modest levels of sFLT01 protein in aqueous, ranging from 32.7 to 112.0 ng/mL (mean ± SD, 73.7 ± 30.5 ng/mL) at Week 26, with decrease to 53.2 ± 17.1 ng/mL) at Week 52.

II. Ongoing Gene Therapy Programs for nAMD

A. RGX-314, an AAV8 vector expressing an anti-VEGF-A Fab similar to ranibizumab[11]

1. Phase 1/2a open-label, dose-ranging trial of subretinal RGX-314

a. 5 dose cohorts

i. 1.3×10^9 ($n = 6$) genome copies (GC)

ii. 1×10^{10} ($n = 6$) GC

iii. 6×10^{10} ($n = 6$) GC

iv. 1.6×10^{11} ($n = 12$) GC

v. 2.5×10^{11} ($n = 12$) GC

b. The primary objective was to evaluate the safety and tolerability of RGX-314 through Week 26, and it was found that subretinal injection of RGX-314 was generally safe and well tolerated. Retinal pigmentary changes (hypo- and hyperpigmentation) were observed on ultrawide-field fundus photographs, fluorescein angiograms, and fundus autofluorescence images mainly in the inferior retina in 27 patients, with dose-related increase in incidence. In cohorts 2-4, pigmentary changes were not seen in the macula and were not associated with clinical symptoms or reduced visual acuity. In Cohort 5, 3 of 9 subjects in whom RGX-314 was injected under retina superior to the superotemporal arcade vessel had pigmentary changes in the macula, and 2 had reduction in visual acuity after pigmentary changes developed.

c. RGX-314 protein was detected 1 month after subretinal injection of RGX-314 in all cohorts and at 2 years after injection; mean aqueous RGX-314 protein levels were substantially higher in cohorts 3 (227.2 ng/mL), 4 (272 ng/mL), and 5 (317.2 ng/mL), compared with cohorts 1 (54.0 ng/mL) and 2 (88.8 ng/mL).

d. Mean baseline BCVA was maintained or improved in cohorts 2-5 through Year 2, while in cohort 1, there was gradual reduction in mean BCVA over time despite frequent rescue injections. Mean CRT was stable or reduced in cohorts 3-5, with mean number of rescue anti-VEGF per year of 2.8, 4.4, and 2.0. Compared to the number of anti-VEGF injections prior to enrollment, the number of anti-VEGF injections per year after injection of RGX-314 was unchanged in cohorts 1 and 2, but markedly reduced in cohorts 3-5.

2. ATMOSPHERE: pivotal Phase 3 trial testing subretinal injection of RGX-314
    a. Treatment arms
        i. Subretinal injection of 6.4 x 10^{10} GC RGX-314 (*n* = 100)
        ii. Subretinal injection of 1.3 x 10^{11} GC RGX-314 (*n* = 100)
        iii. Monthly injections of 0.5-mg ranibizumab (*n* = 100)
    b. Primary endpoint: mean change from baseline BCVA at Week 54
3. AAVIATE: Phase 2 trial testing suprachoroidal injection of RGX-314
    a. Treatment arms
        i. 2.5 x 10^{11} GC RGX-314
        ii. 5.0 x 10^{11} GC RGX-314
        iii. Monthly injections of 0.5-mg ranibizumab
    b. Primary endpoint: mean change from baseline BCVA at Week 40

B. ADVM-022, an AAV.7m8 vector that expresses aflibercept

OPTIC trial: open-label, dose-escalation trial

1. Treatment arms
    a. Cohort 1: Intravitreous injection of 6 x 10^{11} GC ADVM-022/13 days oral steroids (*n* = 6)
    b. Cohort 2: Intravitreous injection of 2 x 10^{11} GC ADVM-022/13 days oral steroids (*n* = 6)
    c. Cohort 3: Intravitreous injection of 2 x 10^{11} GC ADVM-022/topical steroids (*n* = 9)
    d. Cohort 4: Intravitreous injection of 6 x 10^{11} GC ADVM-022/topical steroids (*n* = 9)
2. Safety
    a. Inflammation sometimes occurring late, high dose > low dose
    b. 2 x 10^{11} GC ADVM-022 selected for future studies
3. Supplemental injections in 2 x 10^{11} GC ADVM-022 at 1 year (*n* = 15)
    a. 85% reduction in number of anti-VEGF injections compared with prior to enrollment
    b. No supplemental injections in 9 of 15 patients (60%)

References

1. Maguire AM, Simonelli F, Pierce EA, et al. Safety and efficacy of gene transfer for Leber's congenital amaurosis. *N Eng J Med*. 2008; 358:2240-2248.
2. Campochiaro PA, Nguyen QD, Shah SM, et al. Adenoviral vector-delivered pigment epithelium-derived factor for neovascular age-related macular degeneration: results of a Phase I clinical trial. *Hum Gene Ther*. 2006; 17:167-176.
3. Campochiaro PA, Lauer AK, Sohn EH, et al. Lentiviral vector gene transfer of endostatin/angiostatin for macular degeneration (GEM) study. *Hum Gene Ther*. 2016; 28:99-111.
4. O'Reilly MS, Boehm T, Shing Y, et al. Endostatin: an endogenous inhibitor of angiogenesis and tumor growth. *Cell* 1997; 88:277-285.
5. O'Reilly MS, Holmgren S, Shing Y, et al. Angiostatin: a novel angiogenesis inhibitor that mediates the suppression of metastases by a Lewis lung carcinoma. *Cell* 1994; 79:315-328.
6. Lai C-C, Wu W-C, Chen S-L, et al. Suppression of choroidal neovascularization by adeno-associated virus vector expressing angiostatin. *Invest Ophthalmol Vis Sci*. 2001; 42:2401-2407.
7. Mori K, Ando A, Gehlbach P, et al. Inhibition of choroidal neovascularization by intravenous injection of adenoviral vectors expressing secretable endostatin. *Am J Pathol*. 2001; 159:313-320.
8. Takahashi K, Saishin Y, Saishin Y, et al. Intraocular expression of endostatin reduces VEGF-induced retinal vascular permeability, neovascularization, and retinal detachment. *FASEB J*. 2003; 17:896-868.
9. Rakoczy EP, Lai C-L, Magno AL, et al. Gene therapy with recombinant adeno-associated vectors for neovascular age-related macular degeneration: 1 year follow-up of a Phase 1 randomized clinical trial. *Lancet* 2015; 386:2395-2403.
10. Heier JS, Kherani S, Desai S, et al. Intravitreous injection of AAV2-sFLT01 in patients with advanced neovascular age-related macular degeneration: a Phase 1, open-label trial. *Lancet* 2017; 389:50-61.
11. Liu Y, Fortmann SD, Shen J, et al. AAV8-antiVEGFfab ocular gene transfer for neovascular age-related macular degeneration. *Mol Ther*. 2017; 26:542-549.

Ocular Inflammation in Retinal Gene Therapies

Glenn Yiu MD PhD

Background

Retinal gene therapies typically employ viral vectors such as adeno-associated viruses (AAVs) to deliver therapeutic genes to target tissues, as they are nonreplicative and nonpathogenic. However, viral vectors may trigger immune responses that can trigger ocular inflammation, thereby limiting gene transfer or transgene expression. Host immune responses include both innate and adaptive immunity that develop in response to viral capsid proteins or to the transgene, which in the case of some optogenetic actuators or bacteria-derived CRISPR-Cas9 systems, may also be foreign in nature. The immunogenicity of viral vectors used in gene therapies may depend on type and dose of the viral vector, the promoter and transgene, the route of delivery, and even the underlying retinal condition.[1]

Outline

In this talk, I will discuss the elements of ocular immune privilege, including the absence of lymphatics, immunological ignorance, blood–ocular barriers, the immunosuppressive environment, and immune deviation. I will discuss how different AAV vectors, doses, and routes of administration have triggered different levels of ocular inflammation in both preclinical large animal studies and human clinical trials, including lessons learned from studies of intravitreal AAV8-RS1 for patients with X-linked retinoschisis and early termination of the Phase 2 INFINITY study using ADVM-022 for diabetic macular edema (DME). Finally, I review the potential immunogenicity of novel routes of vector delivery, such as suprachoroidal injection using microneedles, and potential strategies to overcome the ocular inflammation associated with retinal gene therapies.

I. Ocular Immune Privilege
   - A. Absence of lymphatics
   - B. Immunological ignorance
   - C. Blood–ocular barriers
   - D. Ocular immune deviation

II. Ocular Inflammation in Gene Therapies
   - A. Viral vectors, dose, and route of delivery
   - B. Inflammation from AAV8-RS1 for X-linked retinoschisis
   - C. Inflammation from ADVM-022 for DME

III. Methods of Overcoming Ocular Inflammation
   - A. New routes of AAV delivery, including suprachoroidal injections
   - B. Novel AAV designs to evade host immunity
   - C. Considerations for treatment prophylaxis and immunotherapy

Reference

1. Mehta N, Robbins DA, Yiu G. Ocular inflammation and treatment emergent adverse events in retinal gene therapy. *Int Ophthalmol Clin*. 2021; 61(3):151-177.

Stem Cell Therapy for Retinal Diseases: Where Are We Now?

Susanna S Park MD PhD

Introduction

Stem cell therapies are being explored in Phase 1 and 2 clinical trials as potential therapy for retinal degenerative conditions, such as inherited retinal dystrophies and AMD, and retinal vascular disorders, such as retinal vein occlusion. The goal of stem cell therapy is to either replace the damaged tissue or repair the damaged tissue. Tissue replacement is the goal using pluripotent stem cells, such as cells derived from embryonic stem cells or induced pluripotent stem cells. Repair of damaged tissue via paracrine trophic effects is the goal of multipotent stem cells, including adult stem cells in our bone marrow and fetal retinal progenitor cells.

Pluripotent Stem Cells

When we think of stem cells, we think of pluripotent cells, that is, cells that have potential to differentiate into any cell of interest. Only embryonic stem cells or induced pluripotent stem cells are truly pluripotent. Pluripotent stem cells cannot be administered without differentiating the cells since they can form teratomas. Thus, all clinical trials using pluripotent stem cells to treat retinal degeneration have used partially differentiated retinal or retinal pigment epithelial (RPE) cells derived from pluripotent stem cells. These cells have been administered into the subretinal space as cell suspension or as monolayer during vitrectomy.

Two Phase 1/2 open-labeled clinical trials have been conducted in eyes with vision loss from atrophic AMD or Stargardt disease using allogeneic RPE cells derived from embryonic stem cells. Both studies showed that this treatment was feasible and relatively well tolerated except for a few eyes that developed epiretinal membrane and some participants who developed side-effects from systemic immunosuppression.[1] Unfortunately, the visual gain noted in the first study was not seen in the second study.[1,2] A group in Japan was successful in creating an autologous RPE cell line from induced pluripotent stem cells. The cells were administered as a monolayer in the subretinal space of a patient with vision loss from exudative AMD and well tolerated for 1 year.[3] However, there was no visual gain, and the study was put on hold due to genetic instability of subsequently generated induced pluripotent stem cells. Currently, there is a Phase 1/2 study in the United States exploring subretinal administration of RPE cells derived from induced pluripotent stem cells and grown in a scaffold in eyes with vision from atrophic AMD.

Intravitreal Multipotent Stem Cells

Multipotent stem cells are cells that can differentiate into some types of cells but not all. Multipotent stem cells may replace some damaged tissue, but most of the regenerative effects of these stem cells are via paracrine effects (ie, secretion of trophic factors). Thus, intravitreal administration is a feasible approach since the stem cells do not have to be present within the damaged layer of the retina.

Intravitreal injection of allogeneic retinal progenitor cells from fetal retina is being explored as treatment for vision loss for retinitis pigmentosa. A Phase 1/2a, open-labeled dose-escalating study showed relative safety except for mild ocular inflammation. Improvement in perimetry was noted, suggestive of efficacy.[4] A Phase 2b double-masked study is ongoing to evaluate efficacy and safety.

Human bone marrow contains CD34+ stem cells and mesenchymal stem cells (MSCs) that are also multipotent and play an important role in tissue repair and maintenance.[5] Both CD34+ stem cells and MSCs have been explored in clinical trials.

A Phase 1 study has been conducted showing that intravitreal injection of autologous CD34+ stem cells is feasible and well tolerated in eyes with retinal degeneration or ischemia.[6] These stem cells were harvested under good manufacturing practice (GMP) conditions and characterized for purity and sterility before the cells are administered in the eye. Currently, 2 Phase 1/2 clinical trials are being conducted to further explore this autologous stem cell therapy. First is a double-masked, randomized study sponsored by NEI exploring this cell therapy in eyes with vision loss from central retinal vein occlusion. Second is an open-labeled study exploring this cell therapy in eyes with retinitis pigmentosa. No safety concerns have been noted in these studies so far.

MSCs are much fewer in number in bone marrow than CD34+ cells but can be expanded easily when grown in tissue culture.[5] MSCs can also be cultured and harvested from adipose tissue and Wharton's jelly. Both autologous and allogeneic MSCs have been administered intravitreally and subretinally and have been associated with abnormal intraocular cell proliferation. Recently, Ozmert and Arsian administered allogenic MSCs in the subtenon space in eyes with retinitis pigmentosa and noted no safety concerns, with improvement or stabilization of vision.[7]

Based on these early phase clinical trials, unregulated fee-for-service "stem cell centers" have popped up throughout the country. These centers administer cells that have not been characterized or properly purified. Several cases of severe irreversible vision loss, sometimes in both eyes, have been reported in literature.[5] As retinal specialists, we should warn our patients to stay away from such unregulated fee-for-service "stem cell centers."

Summary

Stem cell therapy for retinal regeneration remains an experimental treatment that should be administered only as part of regulated and closely monitored clinical trials and using cells harvested and manufactured under GMP conditions. The full safety and potential efficacy of this novel approach to retinal regeneration is still unknown and continues to be investigated in clinical trials.

References

1. 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; 385:509-516.
2. Mehat MS, Sundaram V, Ripamonti C, et al. Transplantation of human embryonic stem cell-derived retinal pigment epithelial cells in macular degeneration. *Ophthalmology* 2018; 125:1765-1775.
3. Mandai M, Watanabe A, Kurimoto Y, et al. Autologous induced stem-cell-derived retinal cells for macular degeneration. *N Engl J Med*. 2017; 376:1038-1046.
4. Singh MS, Park SS, Albini TA, et al. Retinal stem cell transplantation: balancing safety and potential. *Prog Retin Eye Res*. 2020; 75:100779.
5. Park SS, Moisseiev E, Bauer G, et al. Advances in bone marrow stem cell therapy for retinal dysfunction. *Prog Retin Eye Res*. 2017; 56:148-165.
6. Park SS, Bauer G, Abedi M, et al. Intravitreal autologous bone marrow CD34+ cell therapy for ischemic and degenerative retinal disorders: preliminary Phase 1 clinical trial findings. *Invest Ophthalmol Vis Sci*. 2015; 56:81-89.
7. Ozmert E, Arsian U. Management of retinitis pigmentosa by Wharton's jelly derived mesenchymal stem cells: preliminary clinical results. *Stem Cell Res Ther*. 2020; 11:25.

Optimizing Submacular Injections: Cell, Viral, and Recombinant Therapeutics

Steven D Schwartz MD

I. History
   A. Surgical access to the submacular space has been practiced and studied for decades.
   B. Formally assessed in the National Eye Institute–sponsored Submacular Surgery Trials (SST)
   C. Delivery of therapeutics became routine with tissue plasminogen activator (TPA).

II. Novel therapeutics such as gene and cell therapies present a new set of surgical challenges.
   A. Precise volume delivery
   B. Precise anatomic delivery
      1. Transvitreal subneurosensory injection
      2. Suprachoroidal injection (not detailed in outline)
      3. Bleb location
   C. Reflux prevention
   D. Perioperative immunosuppression

III. Surgical Considerations
   A. Complete vs. partial posterior vitreous detachment (PVD) induction: Recommend surgical induction of PVD to prevent retinal detachment; traction at retinotomy site regardless of age of patient
      1. Pediatric patients can present a challenge, but PVD remains important.
      2. Elderly patients can have attached posterior hyaloid, and thus PVD should be confirmed or created. SST demonstrated significant number of adult and elderly patients without PVD.
      3. Ideally, PVD should be completed to posterior border of vitreous base or as anterior as safely possible. Important to recognize and treat retinal breaks.
   B. Instruments
      1. MedOne microcannulae
      2. 25 gauge to 28-gauge flexible tip
         a. Some surgeons prefer to trim the tip to create a beveled edge; the disadvantage is the tip becomes sharp.
         b. Some surgeons prefer microjet-like delivery.
      3. 25-gauge to 38-gauge curved metal cannula, easier access, directed flow
      4. 25-gauge to 35-gauge: Heavier fluidics may explain atrophy induction.
   C. Internal coating of syringe, extension tubing, cannula may bind viral vectors and decrease effective dose delivery.
   D. Turbulence may damage cell-based product and decrease effective dose delivery.
   E. Manual, assistant-driven injection with skilled assistant slowly driving injection less than ideal
   F. Pedal-driven, surgeon-controlled pump provides better control and precision. MedOne microdose kit and vitrectomy console pump provides surgeon-controlled pedal-driven pump.
      1. Recommend 16-18 psi with IOP set at 10
      2. Recommend very slow injection over 45-60 seconds
      3. Observe bleb formation in real time to make certain bleb is forming in desired location and direction.
      4. Consider second bleb if formation of primary bleb is suboptimal.
      5. For macular gene therapy, typical preferred location is superior macula.
      6. For cell therapy trials, each trial has proscribed location criteria.
      7. Each therapeutic has designated injection volume (Luxturna 300, microliters; cell therapies, 150 microliters and up depending on the trial).
   G. Viewing system for injection should be surgeon preference.
      1. Wide-field viewing (AVI or Resight Yellow) allows optimal instrument location in preretinal space and excellent visualization of bleb formation.
      2. High magnification (drop on contact) allows optimal cannula-retina interface viewing with better depth perception and increased confidence of subneurosensory injection.
      3. Intraoperative OCT provides additional data; surgeon preference. Most surgeons feel it is nice to have but not necessary for precise submacular injection as the data is very rarely used in real time. OCT confirmation of bleb location is typically after the fact.

H. Direct injection of therapeutic vs. "prebleb" creation with BSS should be surgeon preference. No "prebleb" recommended.

Disadvantages of "prebleb" creation include increased gape at retinotomy site with reinjection through same retinotomy, yielding subsequent increased reflux of therapeutic into preretinal space; decreased efficiency of bleb creation; increased turbulence within bleb.

I. Air–fluid exchange should be at surgeon's discretion; recommend complete air–fluid exchange.

1. Complete air–fluid exchange loculates therapeutic material in submacular space.
2. Complete air–fluid exchange can remove refluxed therapeutic from preretinal space, diminishing off-target effects such as inflammation and proliferation.
3. Air–fluid exchange can prevent postoperative hypotony and obviate the need for sutured closure of incisions.
4. Trailing air bubble within the bleb should be avoided as it rarely tamponades retinotomy and can adversely interact with gene therapy vector or cell therapy materials.

J. Postoperative positioning should be as proscribed for each therapeutic. Typically patients are supine for 6-24 hours postoperatively to facilitate bleb resorption and mitigate postoperative reflux into preretinal space.

IV. Future: Robotic Submacular Injection

A. Surgeon assisted: Precise (Ziess)

B. Automated: Horizon Surgical

Solving the Last Mile Problem: Training Deep Learning Models to Work With New Retinal Imaging Devices Without Human Annotations

Aaron Y Lee MD

Generalizing deep learning models trained on a source domain to different target domains by unsupervised cross-domain learning

Artificial intelligence has transformed the field of medical image analysis. In ophthalmology, deep learning models have been developed to diagnose diabetic retinopathy, glaucoma, and AMD. But several challenges remain. Deep learning models require expert input to label the training data, which is costly and time-consuming. Also, generalizability is a problem: a model trained on 1 dataset may not perform well on data from different hospitals, imaging protocols, and device manufacturers. Transfer learning is a potential solution to the generalizability problem, but transfer learning still requires expert-labeled data and retraining.

Our new approach is to use domain adaptation, where generative adversarial networks (GANs) generate synthetic images of the labeled data from the source domain in the target domain. The GAN preserves the structural information of the labeled data but changes the look and feel of the image to match the target domain. We combined a domain adaptation GAN with a U-Net segmentation algorithm into 1 model in order to segment retinal layers on OCT images. The GAN and the segmentation network are trained end to end to improve generalization performance across different OCT devices.

Our datasets included images from 4 different OCT devices: Heidelberg, Topcon 1000, Zeiss Plex Elite 9000, and Topcon Maestro2. The source domain included 110 OCT Heidelberg B-scans and the corresponding labels for intraretinal fluid (IRF) and 7 retinal layers (manually labeled by experts from Duke University). Our target domain included 1112 unlabeled training images from Topcon 1000 B-scans. We also created an external test set consisting of 55 Topcon 1000 B-scans, manually segmented by expert graders from Moorfields Eye Hospital.

The GANSeg model included a GAN plus a supervised U-Net model trained end to end, so that the GAN trained the segmenter to be proficient on images of type A, images with A content but B style (A2B), and finally reconstructed images with A content and A style (A2B2A). The comparator model, U-Net, was trained on Heidelberg images only.

First, we compared GANSeg and U-Net performance on 11 held-out Heidelberg B-scans to Duke grader 1. Next, the performance of both models on 55 Topcon 1000 B-scans was compared against Moorfields grader 1. Finally, GANSeg and U-Net performance on 3 B-scans each from Zeiss Plex Elite 9000 and Topcon Maestro2 was assessed.

GANSeg and U-Net performed comparably in terms of intersection over union (IOU) to the human graders (Duke) on the held-out test Heidelberg B-scans for all classes. However, only GANSeg generalized to the Topcon 1000 B-scans, significantly outperforming the U-Net on this task. GANSeg's IoUs on the Topcon 1000 images were within the IoU range of the interobserver IoUs of the Moorfields graders. GANSeg also performed well on the Zeiss Plex Elite 9000 and Topcon Maestro2 B-scans, while U-Net did not. Both models performed less well on IRF segmentation, although the human graders also demonstrated significant variability when labeling IRF.

To our knowledge, this is the first implementation of unsupervised cross-domain deep learning applied to macular OCT images across different device manufacturers. GANSeg was completely unsupervised with respect to the target domain: no labeled Topcon 1000 data was used to train the model. The unlabeled Topcon 1000 B-scans helped the GAN component learn the Topcon 1000 style so that it could be applied to the Heidelberg scans. GANSeg then augmented the training dataset by pairing Heidelberg labels with Heidelberg scans in the style of Topcon 1000, allowing the U segmenter to perform well on both Heidelberg and Topcon 1000 styles.

The combination design of the model is unique. We explicitly enforced that GANSeg's GAN style generators allow the U segmenter to segment the layers of the Heidelberg scans in the style of Topcon 1000 in the same anatomical positions by propagating the loss end to end. In addition to the Topcon 1000 B-scans, GANSeg was able to generalize to B-scans from the Zeiss Plex Elite 9000 and Topcon Maestro2, both swept source OCT devices, without the need for any additional training or fine-tuning, or any labeled data from the new devices. Overall, these results suggest that we can transfer data across domains, thus greatly increasing the generalizability of deep learning algorithms for supervised tasks such as classification and segmentation.

Application of AI in Predicting Cardiovascular and Neurological Diseases From Eye Images

Tien Y Wong MBBS

I. Introduction

Direct observation and imaging of the vascular and neurological systems can be achieved via imaging structures in the eye. For decades, researchers have used the noninvasive nature of eye imaging, particular color fundus photographs (CFPs), and OCT to examine changes in the retina as a possible marker of cardiovascular disease (CVD) and a spectrum of neurological diseases, such as stroke and dementia. Building on these studies, the application of artificial intelligence deep learning (AI-DL) on CFP and OCT has advanced this field further with significant new data. Figure 1 shows a framework for using AI to predict CVD and neurological diseases from eye images.

II. Current Evidence

A. Using AI to estimate systemic risk factors from eye images

AI-DL has been used on CFP for the prediction of systemic risk factors, including demographic and lifestyle factors.

1. Range: In a landmark paper by the Google group, Poplin et al predicted a range of systemic risk factors from CFP via AI-DL and even used the results to predict CVD events over 5 years in the UK Biobank.[1]
2. Age and sex: With respect to individual risk factors, age can be accurately predicted from CFP via AI-DL.[1,2] In addition to age, the ability to identify sex from CFP via AI-DL has also been demonstrated. For example, Rim et al showed good results in predicting age (coefficient of determination, R^2 = 0.36-0.63) and sex (area under a curve [AUC] = 0.80-0.91) from CFPs.[3]
3. Smoking: In terms of other risk 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]
4. BMI: BMI has also been predicted from CFP via AI-DL, although there is greater variability, with a low generalizability across the ethnic groups.[2]

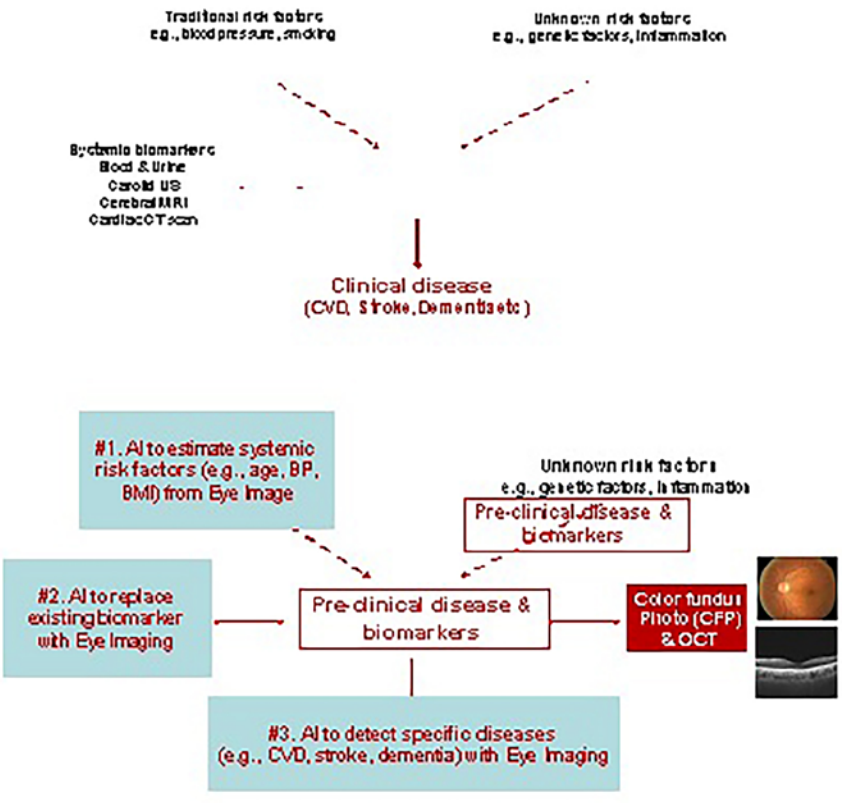

Figure 1. Framework for predicting cardiovascular and neurological diseases from eye images.

B. Using AI to replace existing biomarker with eye imaging

Some studies have used AI-DL technology applied to CFP to replace an existing biomarker of CVD.

1. Coronary artery calcium (CAC): A preclinical marker of atherosclerosis, CAC is strongly associated with risk of clinical CVD. Rim et al developed an AI-DL model to predict CAC from CFP (termed "RetiCAC") with external validation of the estimated CAC (RetiCAC) in predicting CVD events in the UK Biobank.[5]
2. Carotid artery atherosclerosis: Chang et al developed an AI-DL model to predict carotid artery atherosclerosis measured by carotid intima media thickness, and the model was able to predict ultrasonographically confirmed carotid artery atherosclerosis with an AUC of 0.713.[6] The study further 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.
3. Retinal vessel diameter: Changes in the retinal vessel diameter have been predictive of CVD and neurological diseases. However, the process for measuring retinal vessel diameter is time consuming, limiting the expansion and wider application of this method. To address these, Cheung et al used AI-DL to measure retinal vessel diameter.[7] This study showed that a narrow retinal arteriolar diameter measured using AI-DL was associated with incident CVD and all-cause mortality in 2 prospective cohorts.

C. Using AI to detect specific diseases with eye imaging

There are fewer studies on using CFP to directly predict CVD and neurological diseases. 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.[8]

III. Future Research

Several groups are evaluating the use of OCT to predict dementia.[9,10]

IV. Conclusion

The eye provides an opportunity to predict systemic disease factors using eye images. Various studies have shown this potential, but further efforts are needed. To date, there remains lack of data on OCT, insufficient prospective studies on CFP, and lack of evidence in real-world settings, and therefore the clinical application of AI-DL models using eye images to predict CVD and neurological disease is promising but not yet ready for clinical application.

References

1. 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.
2. Nusinovici S, Rim TH, Yu M, et al. Retinal photograph-based deep learning predicts biological age, and stratifies morbidity and mortality risk. *Age Ageing*. 2022; 51(4):afac065.
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. 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.
5. 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.
6. 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.
7. 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.
8. 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.
9. 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.
10. Wagner SK, Hughes F, Cortina-Borja M, et al. AlzEye: longitudinal record-level linkage of ophthalmic imaging and hospital admissions of 353157 patients in London, UK. *BMJ Open*. 2022; 12(3):e058552.

Defining the Fluid Problem in Neovascular AMD: To Dry, or Not to Dry?

Justis P Ehlers MD

I. Background on Treatment Strategies
   Fluid-targeted individualized therapy
II. Review of Fluid Features
   A. Exudative
   B. Degenerative
III. Traditional Impact of Fluid on Visual Acuity
   A. Intraretinal fluid
   B. Subretinal fluid
IV. New Insights on Fluid Impact on Outcomes
   A. Compartmental fluid volatility
   B. Sequelae of fluid instability
V. Outer Retinal Integrity and Impact on Visual Acuity
   Possible missing link to the dry vs. wet discussion
VI. Impact on Therapeutic Decision-Making

Deep Learning for Biomarkers in Non-neovascular AMD

Srinivas Sadda MD

I. Evolution of Biomarkers and Endpoints in Geographic Atrophy (GA) Trials
   A. Past: color fundus photos
   B. Present: fundus autofluorescence (FAF)
   C. Future: OCT
II. Correlation Between FAF and OCT
   A. Area of definitely decreased AF (DDAF) on FAF images and area of hypertransmission on en face OCT show good agreement.
   B. Although GA measured by FAF and OCT are highly correlated, they may be not measuring exactly the same thing.
   C. Historical limitation of OCT: Lack of consensus on definitions of atrophy
III. Classification of Atrophy Meeting (CAM) Definitions of Atrophy on OCT
   A. Complete retinal pigment epithelium (RPE) + outer retinal atrophy: cRORA
      1. Hypertransmission of ≥250 micrometers
      2. Zone of attenuation/disruption of RPE ± basal lamina (BL) complex of ≥250 μm
      3. Evidence of overlying photoreceptor degeneration whose features include all of the following:
         a. Outer nuclear layer thinning
         b. External limiting membrane loss
         c. Ellipsoid zone/interdigitation zone loss
      4. No signs of RPE tear
   B. Incomplete RPE + outer retinal atrophy: iRORA
      1. Some hypertransmission must be present, but often discontinuous.
      2. Some irregularity of RPE ± BL complex
      3. Detectable photoreceptor degeneration, signs of which can include "wedge" and "subsidence"
      4. Does not fulfill criteria for cRORA
   C. Preventing conversion from iRORA to cRORA may be an early intervention approach for dry AMD therapies.
   D. Challenges, especially for grading iRORA
      1. Requires time-consuming assessment by trained graders
      2. Moderate reproducibility for some relevant features such as RPE disruption
IV. Deep learning approaches may enhance our ability to grade iRORA and cRORA.
   A. Potential challenges in using an AI approach
      1. AI models typically require many 1000s of training data.
      2. Limited volumetric OCT data with iRORA and cRORA annotations for use in model training
   B. Solution
      1. Slice integration of volumetric features extracted by pre trained residual neural networks: SLIVER-net (UCLA Computational Medicine)
         a. A general approach for analyzing 3-D medical images
         b. Applicable to MRI, CT, ultrasound, OCT
         c. Transfer learning via image transformation
         d. Transfer learning source: Kermany et al, UCSD. 84,495 fovea-centered B-scans from various diseases.
         e. Key characteristics of SLIVER-net
            i. 3-D OCT volume → 2-D "tiling" (eg, mosaic) of slices, allowing use of transfer learning with currently available 2-D data
            ii. Additional layers of the deep neural network enable SLIVER-net to preserve the 3-D spatial structure lost by tiling ("secret sauce").
            iii. Despite a limited training set, SLIVER-net performance exceeded that of 3D-CNNs.

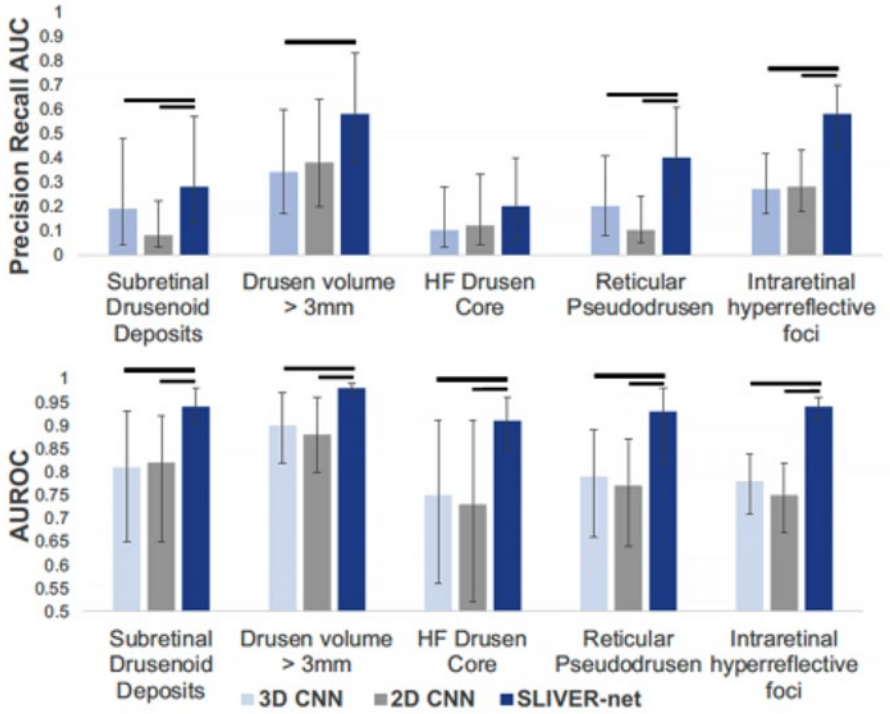

Figure 1

2. ResNet18
    a. Annotation of datasets by reading center graders for iRORA/cRORA
    b. Two data sources for training:
        i. >101 OCT volumes (6138 B-scans) from 37 subjects with intermediate AMD/late AMD with iRORA and/or cRORA
        ii. >87 OCT volumes (4128 B-scans) from 34 subjects with early/intermediate AMD without iRORA/cRORA (control set)
    c. Testing Set #1, Amish Eye Study: 1117 OCT volumes (108,289 B-scans) from 649 Amish subjects ("OCT volume level")
    d. Testing Set #2, Retina Clinic: 60 OCT B-scans from 60 subjects with AMD ("OCT B-scan level")

3. Results
    a. Attention/heat maps for individual OCT B-scans demonstrated proper localization to atrophic lesions when present.
    b. Heat maps for OCT B-scans from healthy maculae show a diffuse signal.
    c. Post hoc review of "incorrect" cases suggested possible grader errors or questionable determinations in most cases.

V. Summary
    A. A machine learning model was developed using a transfer learning paradigm to identify iRORA and cRORA with reliability similar to that of expert human graders.
    B. The model was developed on a relatively small dataset.
    C. Good performance was observed in 2 different datasets from 2 different types of data sources (population based vs. clinic).

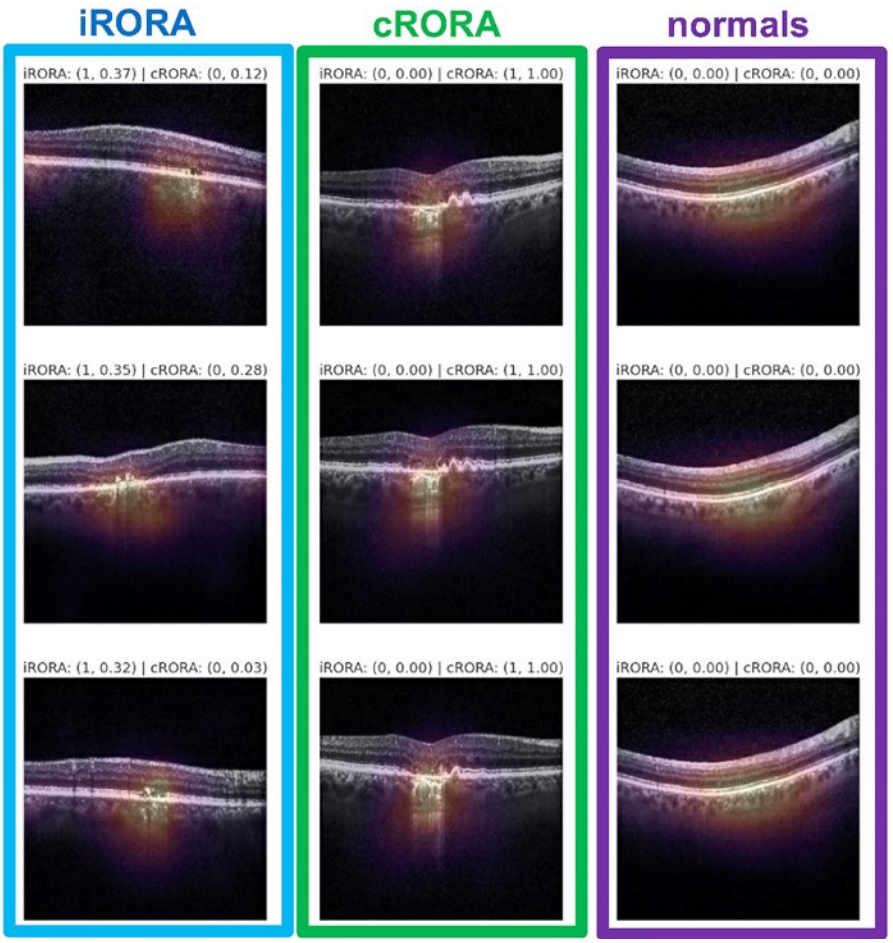

Figure 2

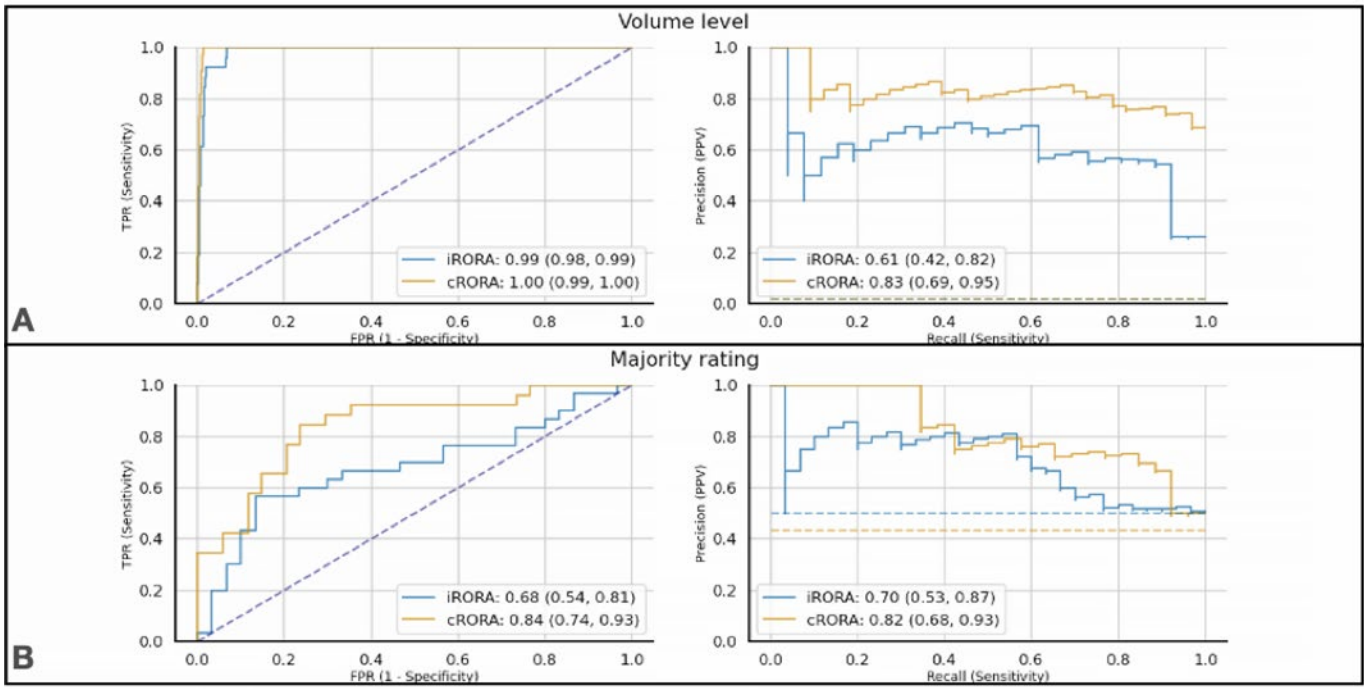

Figure 3

The Role of AI-Guided OCT Imaging in Geographic Atrophy

Ursula Schmidt-Erfurth MD

Of all AMD patients, 85%-90% are affected by the nonneovascular AMD type, which results in at least 1 million patients in the United States and 8 million geographic atrophy (GA) patients worldwide. Severe vision loss, however, only occurs at a late stage of the disease. In the absence of reliable functional markers, clinical studies have used GA lesion growth, an anatomical endpoint, to investigate disease progression and the efficacy of therapeutic interventions.

With the advent of therapeutic proof-of-principle in randomized clinical trials comes a strong need to identify optimal imaging methods for monitoring disease activity and therapeutic efficacy. Conventionally, fundus autofluorescence (FAF) has been considered the standard imaging modality. FAF provides a 2-dimensional en face representation, with hypoautofluorescence indicating retinal pigment epithelium (RPE) loss.

Compared to 2-dimensional FAF imaging, spectral domain OCT (SD-OCT), acquired as a volume of cross-sectional scans, provides a 3-dimensional morphology of the affected retinal layers. Previous studies showed that measurements of GA areas by OCT and FAF correlate well. But FAF must be replaced by OCT to assess the photoreceptor status.

Effect of Treatment on Photoreceptor Maintenance in GA Monitored by AI-Based OCT Analysis

We investigated the therapeutic effect of intravitreal pegcetacoplan on the inhibition of photoreceptor (PR) loss and thinning in GA on conventional SD-OCT imaging by deep learning–based automated PR quantification. We performed fully automated, deep learning–based segmentation of retinal pigment epithelium (RPE) loss and PR thickness on SD-OCT volumes (Spectralis) acquired at baseline and Months 2, 6, and 12. The difference in the change of PR loss area was compared between treatment arms, as was the change in PR thickness adjacent to the GA borders and in the whole 20-degree scanning area. A total of 31,556 B-scans of 644 SD-OCT volumes of 161 study eyes (monthly [AM]), 52; bimonthly [AEOM], 54; sham [SM], 56) were evaluated from baseline to Month 12. Comparison of mean change in PR loss area revealed statistically significantly less growth in the AM group at Months 2, 6, and 12 compared to SM (–41 µm ± 219 vs. 77 µm ± 126; $P = .0004$ / –5 µm ± 221 vs. 156 µm ± 139; $P < .0001$ / 106 µm ± 400 vs. 283 µm ± 226; $P = .0014$). Furthermore, PR thinning was significantly reduced under AM pegcetacoplan treatment compared to SM within the GA junctional zone as well as throughout the 20-degree area.

Distinct and reliable quantification of PR loss using deep learning–based algorithms offers an essential tool for evaluating therapeutic efficacy in slowing disease progression. PR loss and PR thinning are reduced by intravitreal complement C3 inhibition. Automated quantification of PR loss/maintenance based on OCT images is an ideal approach to reliably monitor disease activity and therapeutic efficacy in the management of GA in clinical routine and trials.

Treatment Effect on Topographical Adjusted Local Progression of GA Quantified With AI

GA progresses slowly, and kinetics have been shown to be highly variable between individual patients and within a patient. GA progression rate has been associated with lesion shape direction toward fovea vs. periphery, topographic locations, PR degeneration, hyperreflective foci (HRF) concentration, junctional zone FAF patterns, subretinal drusenoid deposits, low-luminance deficit, and surrounding choriocapillaris flow deficits.

We investigated also the effects of intravitreal pegcetacoplan treatment on spatially resolved heterogeneous progression of GA with respect to topographic and structural properties quantified in SD-OCT images by deep learning. Patients with GA secondary to AMD (FILLY, NCT02503332) were included, 312 SD-OCT scans of 57 eyes with monthly, 46 eyes with every-other-month (EOM) treatment, and 53 eyes with sham (SM) injection from baseline and 1 year follow-up. RPE loss, PR layers, and HRF were automatically segmented using deep learning algorithms. GA local progression rate (LPR) was determined from a level-set based growth model that measured the local expansion of GA margin from the delineated en face projections from baseline to 1 year. For each GA margin point, the eccentricity to the fovea center, the progression direction (toward fovea vs. periphery), the mean PR thickness, and the HRF concentration in the junctional zone within a 800-µm radius were computed. Mean LPR and treatment effect conditioned on these properties were estimated by nonlinear regressions based on spatial generative additive mixed-effect models (GAMM). A total of 31,527 local GA margin points were analyzed.

Overall, LPR was higher for areas with low eccentricity, thinner PR layer thickness, or higher HRF concentration in the proximity of GA margin point. For progression toward fovea, highest LPR was around 1 mm eccentricity. When controlling for topographic and structural risk factors, we reported a significantly lower LPR, by –28.0% (95% CI, –42.8 to –9.4; $P = .0051$) and –23.9% (95% CI, –40.2 to –3.0; $P = .027$) for monthly and EOM treated eyes, respectively, compared to SM. Furthermore, we observed a trend in treated eyes for higher reduction in LPR for local areas progressing toward fovea. Hence, assessing GA progression on a local level enables us to capture heterogeneity in GA progression in more detail and provides observation of treatment effects accounting for topography and local structural risk factors. Eyes treated with pegcetacoplan showed a significantly slower GA lesion progression rate compared to sham, and an even slower growth rate toward the fovea. Findings from this study may help to identify patient subcohorts with faster progressing lesions, in which pegcetacoplan treatment would be particularly beneficial.

Conclusion

We provided a detailed analysis of spatially densely resolved GA progression under treatment. We were able to explain highly nonuniform growth by the topographic properties eccentricity of GA margin and progression direction, as well as by the structural properties PR status and HRF. Identifying risk factors that influence GA progression with high precision in an automated fashion in SD-OCT images and combining them with spatial nonlinear regression models allows us to adjust the estimation of treatment effect for these factors, and thus obtain more certainty in interpreting to which extent GA growth is slowed by treatment. Importantly, these findings may help us to identify patient cohorts with a higher risk of faster GA progression, such as patients in which treatment would be expected to be highly beneficial.

What the Retina Specialist Should Know About Activities at the NEI in 2022

Michael F Chiang MD

What is the National Eye Institute (NEI)?

The 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 $863 million. The NEI Strategic Plan (published in November 2021 for the first time since 2012) outlines our directions and priorities over the next 5 years.

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)

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

- NEI core research programs currently organized by anatomy and disease: retina; cornea; lens; glaucoma and optic neuropathy; strabismus, amblyopia, and visual processing; low vision
- The 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 and disparities.
- Examples of potential innovations in each area of emphasis (see Figure 1)

What in the NEI Strategic Plan may be of particular interest to retina specialists?

- NIH–Accelerating Medicines Partnership (AMP) Bespoke Gene Therapy Consortium: public-private partnership
- Regenerative medicine initiatives: cell-based therapies, gene editing
- Artificial intelligence and data science initiatives, including Bridge2AI, AIM-AHEAD
- Data sharing and data harmonization initiatives
- Quality-of-life initiatives: patient-related quality-of-life measures, improving accessibility of home COVID-19 testing by visually impaired patients
- Population health: initiatives to strengthen vision workforce by increasing pipeline of underrepresented groups in medicine

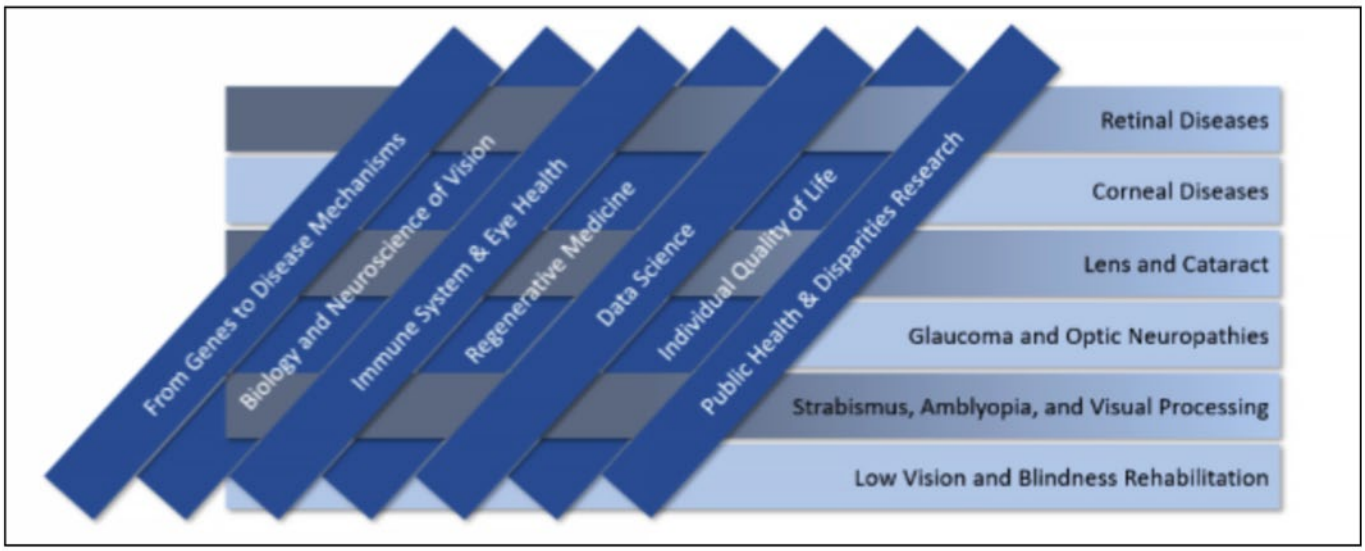

Figure 1. Seven cross-cutting areas of emphasis in the NEI Strategic Plan. These do not replace the existing core program structure but, rather, highlight evolving areas that will require interdisciplinary approaches.

Why Does Drusen Regression Herald Geographic Atrophy?

Mark W Johnson MD, Qitao Zhang PhD, and Jason M L Miller MD PhD

I. Background

A. Regression of drusenoid pigment epithelial detachment (PED) is often rapidly followed by the onset of geographic atrophy (GA), and the rate of PED collapse is proportional to its size.[1]

B. Similarly, regression of submacular vitelliform material is often followed by GA.

C. Healthy retinal pigment epithelial (RPE) cells are constantly secreting lipoprotein particles (LPs), and apolipoprotein E (ApoE) is the primary apolipoprotein on both the apical and basal side of the RPE cell.

D. In early AMD, LP secretion results in accumulation of drusen and subretinal drusenoid deposits (SDDs).

II. Why does drusen regression predict the onset of GA and vision loss?

A. "Drusen ooze" hypothesis[2]

1. Drusen components escape into the outer retina.

2. RPE's attempt to clear the "ooze" overwhelms its phagocytic activity, triggering cell death and GA.

B. Decreased production hypothesis[1,3]

1. Drusen are built with molecular components secreted by RPE.

2. As RPE sickens and degenerates, production of drusen material declines, leading to drusen regression just before GA emerges.

III. Study Hypotheses

A. Drusen regression preceding GA is due to a decrease in production of drusen components by dysfunctional/dying RPE.

B. Vitelliform regression preceding GA is due to a decrease in production of photoreceptor-derived material (vitelliform material) by a dysfunctional photoreceptor-RPE complex.

IV. Methods[4]

A. We used primary mature human RPE cell cultures that replicate many features of in vivo RPE.

B. RPE cells oxidatively stressed with increasing doses of peroxide for 24 hours show:

1. A decrease in RPE tight junction integrity (marker for RPE dysfunction)

2. An increase in cell death

C. ApoE secretion decreases at a concentration of peroxide where neither tight junction disruption nor cell death is noted.

D. The decrease is more prominent on the basal compared to the apical side for all concentrations.

V. Discussion

A. Our RPE culture data

1. Suggest that secretion of ApoE, a major component of drusen/SDDs, decreases prior to generalized RPE dysfunction or death

2. Support the hypothesis that drusen regression results from decreased production of "building material" by sick but not yet dead RPE

B. Thus, drusen disappearance heralds worsening RPE health and eventual GA.

C. Other evidence that declining RPE health leads to drusen regression

1. RPE attenuation is associated with early stages of drusen regression.[5]

2. Collapse of drusenoid PED is preceded by signs of RPE degeneration (eg, hyperreflective foci and disintegration of RPE band).[6,7]

D. Corollary hypothesis

1. Nonspontaneous drusen regression induced by other mechanisms (eg, low-intensity laser treatment, high-dose statins) might *not* be followed by GA.

2. In the Complications of AMD Prevention Trial (CAPT), laser-induced drusen regression was not associated with a higher incidence of GA.[8]

VI. Conclusions

A. Progressive RPE dysfunction results in reduced secretion of ApoE, the major apolipoprotein in both drusen and SDDs.

1. The decline in secretion is greater on the basal (sub-RPE) compared with the apical (subretinal) side.

2. Thus, drusen regress while SDDs initially persist.

B. Similarly, worsening photoreceptor stress results in outer segment shortening, which may reduce/eliminate vitelliform production.

C. Thus, both drusen and vitelliform regressions preceding GA likely are caused by the inability of progressively sickened retina–RPE complex to produce building material.

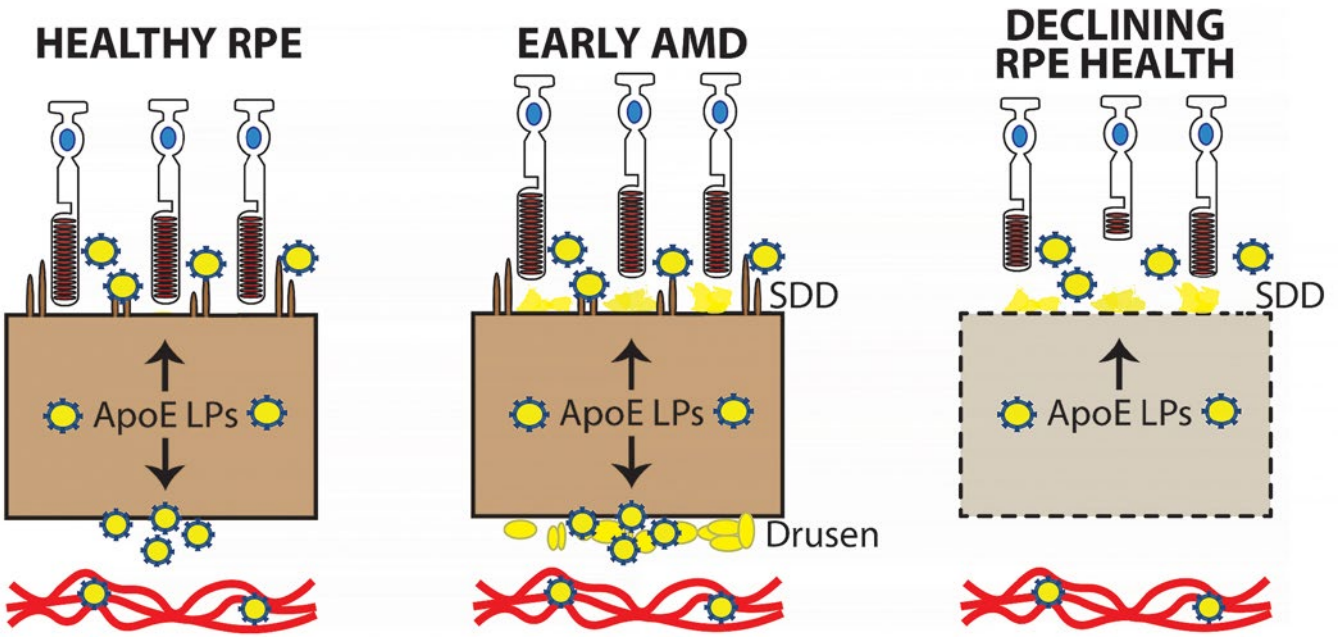

Figure 1

Selected Readings

1. Balaratnasingham C, Yannuzzi LA, Curcio CA, et al. Associations between retinal pigment epithelium and drusen volume changes during the lifecycle of large drusenoid pigment epithelial detachments. *Invest Ophthalmol Vis Sci*. 2016; 57:5479-5489.
2. Mones J, Garcia M, Biarnes M, et al. Drusen ooze: a novel hypothesis in geographic atrophy. *Ophthalmol Retina*. 2017; 1:461-473.
3. Spaide FR, Ooto S, Curcio CA. Subretinal drusenoid deposits AKA pseudodrusen. *Surv Ophthalmol*. 2018; 63:782-815.
4. Miller JML, Zhang Q, Johnson MW. Regression of drusen or vitelliform material heralding geographic atrophy: correlation between clinical observations and basic science. *Graefes Arch Clin Exp Ophthalmol*. 2021; 259:2051-2053.
5. Sarks JP, Sarks SH, Killingsworth MC. Evolution of geographic atrophy of the retinal pigment epithelium. *Eye* 1988; 2:552-577.
6. Balaratnasingam C, Messinger JD, Sloan KR, et al. Histologic and optical coherence tomographic correlates in drusenoid pigment epithelium detachment in age-related macular degeneration. *Ophthalmology* 2017; 124:644-656.
7. Zhang Q, Miller JML. Basic-science observations explain how outer retinal hyperreflective foci predict drusen regression and geographic atrophy in age-related macular degeneration. *Eye (Lond)*. 2022; 36(5):1115-1118.
8. Complications of Age-related Macular Degeneration Prevention Trial Research Group. Laser treatment in patients with bilateral large drusen: the Complications of Age-related Macular Degeneration Prevention Trial. *Ophthalmology* 2006; 113:1974-1986.

Macular Atrophy With Long-term Continuous vs. Bolus Anti-VEGF Therapy in Eyes With Neovascular AMD

Prevalence, Incidence, and Progression of Macular Atrophy in Eyes With Neovascular AMD Over 2 Years in the Phase 3 Archway Trial of the Port Delivery System With Ranibizumab

Glenn J Jaffe MD

Background

Neovascular AMD (nAMD) is a leading cause of blindness globally.[1] Intravitreal anti-VEGF therapy, such as ranibizumab, is the standard of care for patients with nAMD.[2,3] However, real-world data suggest that vision outcomes with anti-VEGF agents in clinical practice have fallen short of those observed in randomized clinical trials due to the requirement for frequent injections and regular patient monitoring, which places a considerable treatment burden on patients.[4,5] Macular atrophy (MA), an irreversible loss of outer retinal tissue and retinal pigment epithelium, can be associated with a variety of diseases, including nAMD.[6] An important clinical question is whether the MA observed in eyes of clinical trial participants is associated with anti-VEGF therapy itself or occurs as part of the natural history of nAMD. To date, most data regarding the development of MA during anti-VEGF treatment have been limited to studies where the anti-VEGF agent has been dosed as a bolus injection into the vitreous.

The Port Delivery System with ranibizumab (PDS; Susvimo) is an innovative drug delivery system that is approved in the United States for the treatment of nAMD.[7] It includes a surgically placed implant that continuously delivers a customized formulation of ranibizumab into the vitreous. The PDS is refilled via clinic-based refill-exchange procedures approximately every 6 months.[7] In the Phase 2 LADDER trial (ClinicalTrials.gov identifier NCT02510794) in nAMD, PDS 100 mg/mL pro re nata was generally well tolerated and showed vision and anatomic outcomes that were comparable with monthly intravitreal ranibizumab 0.5-mg injections (monthly ranibizumab); incidence or enlargement of MA was also similar across these treatment arms.[8]

The current analysis focuses on Archway (ClinicalTrials.gov identifier NCT03677934), a Phase 3 trial in nAMD, in which PDS 100 mg/mL with fixed refill-exchanges every 24 weeks (PDS q24w) demonstrated noninferiority and equivalence in efficacy to monthly ranibizumab (as measured by the change from baseline in BCVA at the average of Weeks 36 and 40).[9] Here we present preplanned exploratory analyses of Archway to determine whether MA differs in eyes with nAMD treated continuously with PDS q24w vs. eyes treated with monthly ranibizumab injections.

Methods

In Archway, PDS q24w was compared with monthly ranibizumab in eyes with nAMD responsive to ≥3 injections of standard-of-care anti-VEGF agents. Patients with subfoveal MA at screening were not eligible to participate in the trial. The analysis population comprised 247 and 167 eyes treated with PDS q24w and monthly ranibizumab, respectively, for a total of 414 eyes. MA was assessed at baseline and Weeks 36, 48, and 96 by masked readers at the Duke Reading Center. MA presence was determined using spectral domain OCT (SD-OCT) images according to Classification of Atrophy Meeting guidelines.[6] MA area was measured on fundus autofluorescence field 2 images; SD-OCT and near-infrared imaging were used to help define MA margins as required. Two readers measured the MA area, and any values differing by >10% were arbitrated by a third reader. Missing data were imputed by worst observation carried forward.

Results

At baseline, MA was observed in 22.3% (55/247) and 20.4% (34/167) of eyes in the PDS q24w and monthly ranibizumab arms, respectively. At Week 96, the prevalence of MA increased to 39.1% of eyes in the PDS q24w arm (90/230), and 39.2% of eyes in the monthly ranibizumab arm (62/158). The mean MA area was similar at baseline for the PDS q24w (1.3 mm^2; 95% CI, 0.4-2.1) and monthly ranibizumab (1.6 mm^2; 95% CI, 0.2-3.0) arms; however, at Week 96, the mean MA area was numerically greater (no statistically significant difference) in eyes treated with monthly ranibizumab than in eyes with PDS q24w (3.6 mm^2; 95% CI, 1.8-5.4) vs. 2.3 mm^2; 95% CI, 1.4-3.1). The mean MA area change from baseline at Week 96 was numerically greater (no statistically significant difference) in eyes treated with monthly ranibizumab (2.9 mm^2; 95% CI, 1.3-4.5) than in eyes treated with PDS q24w (1.6 mm^2; 95% CI, 1.0-2.3). In an analysis of eyes without any MA at baseline (not prespecified), the proportions of eyes that went on to develop MA at Week 96 were similar between the PDS q24w (20.0% [35/175]) and monthly ranibizumab (22.6% [28/124]) arms, showing that incident MA was similar between arms.

Discussion

In these prespecified analyses of Archway, continuous delivery of ranibizumab with the PDS over 96 weeks was not associated with an increased prevalence or incidence of MA compared with monthly ranibizumab injections. In addition, the MA area at Week 96 showed a numerically greater, but not statistically significantly different, increase with monthly ranibizumab injections vs. PDS q24w. This observation warrants further investigation of the data.

References

1. Flaxman SR, Bourne RRA, Resnikoff S et al; Vision Loss Expert Group of the Global Burden of Disease Study. Global causes of blindness and distance vision impairment 1990-2020: a systematic review and meta-analysis. *Lancet Glob Health*. 2017; 5(12):e1221-e1234.
2. American Academy of Ophthalmology Preferred Practice Pattern Retina/Vitreous Committee; Flaxel CJ, Adelman RA, Vemulakonda GA, et al. Age-related macular degeneration Preferred Practice Pattern®. www.aao.org/preferred-practice-pattern/age-related-macular-degeneration-ppp. Posted October 2019.
3. Schmidt-Erfurth U, Chong V, Loewenstein A, et al; European Society of Retina Specialists. Guidelines for the management of neovascular age-related macular degeneration by the European Society of Retina Specialists (EURETINA). *Br J Ophthalmol*. 2014; 98(9):1144-1167.
4. Kim LN, Mehta H, Barthelmes D, Nguyen V, Gillies MC. Meta-analysis of real-world outcomes of intravitreal ranibizumab for the treatment of neovascular age-related macular degeneration. *Retina* 2016; 36(8):1418-1431.
5. 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.
6. Sadda SR, Guymer R, Holz FG, et al. Consensus definition for atrophy associated with age-related macular degeneration on OCT: Classification of Atrophy report 3. *Ophthalmology* 2018; 125(4):537-548.
7. Susvimo [prescribing information]. South San Francisco, CA: Genentech; 2022.
8. Jaffe GJ, Cameron B, Kardatzke D, Ives J, Barteselli G, Gune S. Prevalence and progression of macular atrophy in eyes with neovascular age-related macular degeneration in the Phase 2 Ladder trial of the Port Delivery System with ranibizumab. *Ophthalmol Retina*. Epub ahead of print 2022 Apr 12. doi:10.1016/j.oret.2022.04.006.
9. Holekamp NM, Campochiaro PA, Chang MA, et al. Archway randomized Phase 3 trial of the Port Delivery System with ranibizumab for neovascular age-related macular degeneration. *Ophthalmology* 2022; 129(3):295-307.

The Role of Novel Functional Assessments in AMD: Only for Clinical Research, or the Future of Clinical Care?

Karl G Csaky MD

Background

At the NEI/FDA Ophthalmic Clinical Trial Design and Endpoints Symposiums in 2007 and in 2016, the FDA identified the expansion of geographic atrophy (GA) as an endpoint for trials in dry AMD.[1,2] Loss of the retinal pigment epithelium (RPE) leading to eventual loss of visual acuity detected by reduced fundus autofluorescence (FAF) appears to be the most reliable method of detecting areas of GA.[3-5] No endpoint has been agreed upon by the FDA for the treatment of dry AMD without GA. But in all cases of AMD, the FDA supports the use of functional assessments as potential endpoints for clinical trials.[2]

Therefore, alternative vision function assessments are now becoming incorporated into ongoing trials,[6,7] and these may eventually be required as a treatment parameter for future approved agents for dry AMD. These functional assessments may detect evidence of anatomic changes known to incur in every stage of dry AMD in the absence of visual acuity changes.[5,8] Continued research into the correlation between anatomic changes in dry AMD as detected by OCT and these alternative vision function tools will be critical.[9-11]

Alternative Vision Function Assessments

At present several newer functional tools are being incorporated into ongoing clinical trials for dry AMD. These include:

Low luminance visual acuity (LLVA)

LLVA is an easy function tool that simply requires that a 2.0 neutral density filter be placed in front of the eye under normal conditions of Early Treatment Diabetic Retinopathy Study (ETDRS) visual acuity testing. Studies have shown that LLVA is decreased in many stages of dry AMD[12,13] and that the extent of low luminance deficit (BCVA-LLVA) correlates to the rate of expansion of GA.[14] This is the one additional functional assessment that is being performed in multiple various clinical trials of dry AMD.[6,7,15]

Mesopic/scotopic microperimetry

It has been demonstrated that rod photoreceptors are preferentially affected before cone cells,[8] leading to the finding of both scotopic and mesopic deficits in patients with dry AMD. Therefore, measuring selective photoreceptor sensitivities could be a useful assessment of these photoreceptor changes.[16,17] Either utilizing white light to measure mesopic sensitivity or using the fact that rod cells are more sensitive to blue light simulation 2-color micrometry can directly quantify rod function. While useful for measuring changes in both rod function and scotoma sizes in GA, these tests are time consuming, difficult to administer, and not reliable in numerous patients with dry AMD.[17]

Dark adaptometry

Based on the observation that thickening and changes in the composition of the Bruch membrane are an early and consistent finding in patients with dry AMD and thus alter the function of the RPE, dark adaptation is altered in patients with varying forms of dry AMD.[18,19] Units able to quantify dark adaptation include the Goldman-Weekers Dark Adaptometer and the AdaptDx (Maculogix; Hummelstown, PA).

The AdaptDx has been most extensively studied in dry AMD patients. This machine measures the ability of the retina to respond to a low luminance spot placed on the retina at various times following light exposure. The curve that is generated (see Figure 1a) indicates the time to light sensitivity of the rods at a time termed the "cone-rod break." This time is progressively

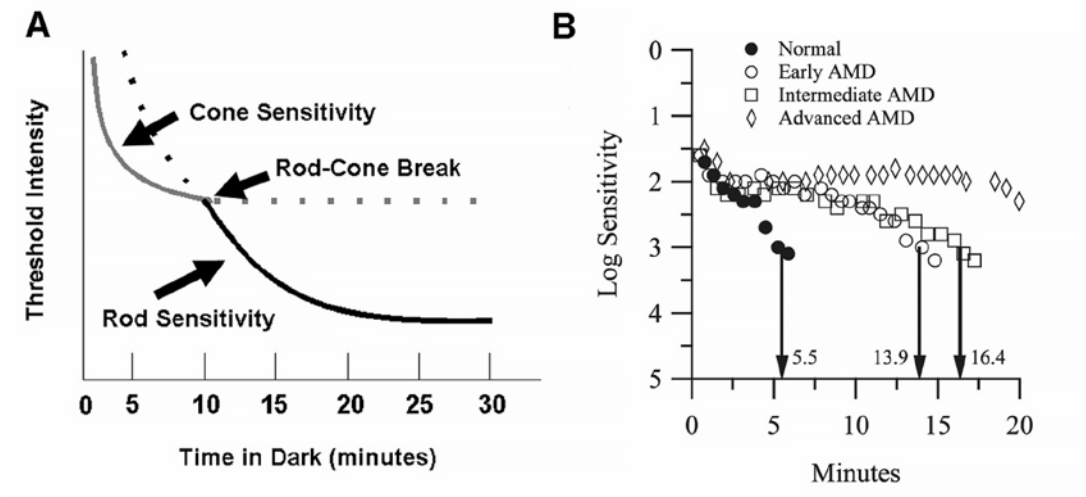

Figure 1. Demonstration of results of dark adaptometry showing (A) the typical break in the slope of initial cone sensitivity to rod sensitivity, which is markedly delayed in advancing forms of dry AMD (B).[18]

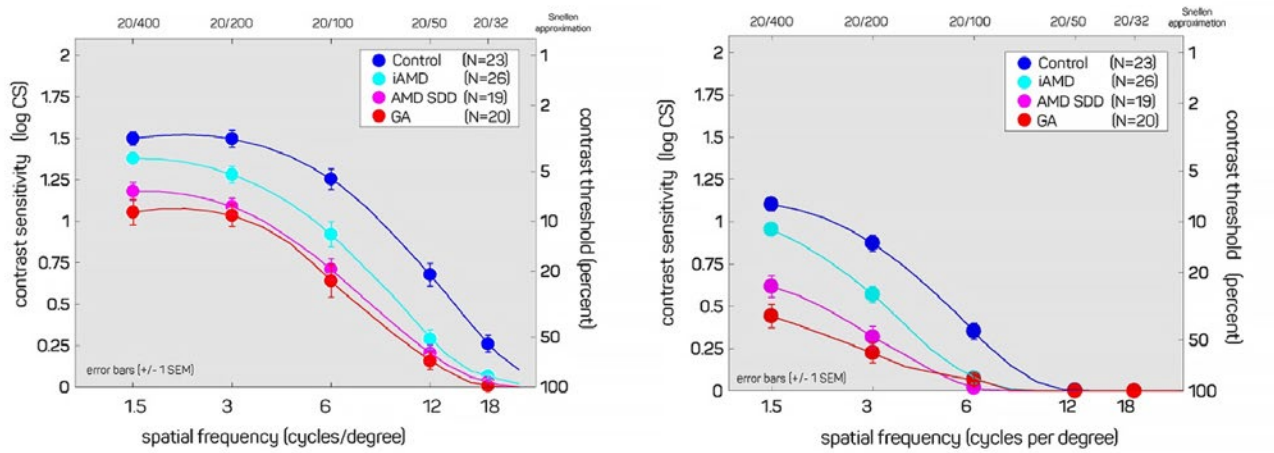

Figure 2. Contrast sensitivity functions measured under standard (left) and low (right) luminance conditions in eyes with varying stages of dry AMD, including intermediate AMD (iAMD), AMD with subretinal drusenoid deposits (AMD SDD), and geographic atrophy (GA), demonstrating stepwise losses between advanced forms of dry AMD. Source: Ou WC, Lesmes LA, Christie AH, Denlar RA, Csaky KG. Normal- and low-luminance automated quantitative contrast sensitivity assessment in eyes with age-related macular degeneration. *Am J Ophthalmol*. 2021; 226:148-155.

delayed in advancing forms of dry AMD (see Figure 1b).[18] Newer research has identified alterations in dark adaptation even in earlier forms of dry AMD.[20] However, the progressive time to end the test in patients with GA and/or with the presence of subretinal drusenoid deposits[21] may make this test impractical for trials of more advanced dry AMD.

Normal and low luminance quantitative contrast sensitivity

While older forms of assessing contrast sensitivity using Pelli-Robson plates proved to be unreliable, a newer automated form utilizing Bayesian algorithms to more quickly and precisely identify contrast sensitivity results in dry AMD patients has shown earlier success.[22] Easy to use by patients and straightforward to administer, this approach captures a large amount of data both on spatial frequencies and contrast sensitivity. In addition, utilizing a standard 2.0 neutral density filter, low luminance automated contrast sensitivity can also be assessed. Preliminary data indicate dissection of varying stages of dry AMD (see Figure 2) can be achieved with good intra- and inter-patient reliability.

References

1. Csaky KG, Richman EA, and Ferris FL. Report from the NEI/FDA Ophthalmic Clinical Trial Design and Endpoints Symposium. *Invest Ophthalmol Vis Sci*. 2008; 49(2):479-489.
2. Csaky K, Ferris F 3rd, Chew EY, Nair P, Cheetham JK, Duncan JL. Report from the NEI/FDA Endpoints Workshop on Age-Related Macular Degeneration and Inherited Retinal Diseases. *Invest Ophthalmol Vis Sci*. 2017; 58(9):3456-3463.
3. Sunness JS, Gonzalez-Baron J, Applegate CA, et al. Enlargement of atrophy and visual acuity loss in the geographic atrophy form of age-related macular degeneration. *Ophthalmology* 1999; 106(9):1768-1779.
4. Schmitz-Valckenberg S, Fleckenstein M, Scholl HP, Holz FG. Fundus autofluorescence and progression of age-related macular degeneration. *Surv Ophthalmol*. 2009; 54(1):96-117.
5. Bird AC, Phillips RL, Hageman GS. Geographic atrophy: a histopathological assessment. *JAMA Ophthalmol*. 2014; 132(3):338-345.
6. Liao DS, Grossi FV, El Mehdi D, et al. Complement C3 inhibitor pegcetacoplan for geographic atrophy secondary to age-related macular degeneration: a randomized Phase 2 trial. *Ophthalmology* 2020; 127(2):186-195.
7. Jaffe GJ, Westby K, Csaky KG, et al. C5 inhibitor avacincaptad pegol for geographic atrophy due to age-related macular degeneration: a randomized pivotal Phase 2/3 trial. *Ophthalmology* 2021; 128(4):576-586.
8. Curcio CA, Medeiros NE, Millican CL. Photoreceptor loss in age-related macular degeneration. *Invest Ophthalmol Vis Sci*. 1996; 37(7):1236-1249.
9. Echols BS, Clark ME, Swain TA, et al. Hyperreflective foci and specks are associated with delayed rod-mediated dark adaptation in nonneovascular age-related macular degeneration. *Ophthalmol Retina*. 2020; 4(11):1059-1068.
10. Ou WC, Denlar RA, Csaky KG. The relationship between central drusen volume and low-luminance deficit in age-related macular degeneration. *Transl Vis Sci Technol*. 2020; 9(4):10.
11. Zhang Y, Sadda SR, Sarraf D, et al. Spatial dissociation of subretinal drusenoid deposits and impaired scotopic and mesopic sensitivity in AMD. *Invest Ophthalmol Vis Sci*. 2022; 63(2):32.
12. McGuinness MB, Fraser RG, Tan R, Luu CD, Guymer RH. Relationship between rod-mediated sensitivity, low-luminance visual acuity, and night vision questionnaire in age-related macular degeneration. *Transl Vis Sci Technol*. 2020; 9(6):30.
13. Wu Z, Ayton LN, Luu CD, Guymer RH. Longitudinal changes in microperimetry and low luminance visual acuity in age-related macular degeneration. *JAMA Ophthalmol*. 2015; 133(4):442-448.
14. Sunness JS, Rubin GS, Broman A, et al. Low luminance visual dysfunction as a predictor of subsequent visual acuity loss from geographic atrophy in age-related macular degeneration. *Ophthalmology* 2008; 115(9):1480-1488.
15. Heier JS, Pieramici D, Chakravarthy U, et al. Visual function decline resulting from geographic atrophy: results from the Chroma and Spectri Phase 3 trials. *Ophthalmol Retina*. 2020; 4(7):673-688.

16. Scholl HP, Bellmann C, Dandekar SS, Bird AC, Fitzke FW. Photopic and scotopic fine matrix mapping of retinal areas of increased fundus autofluorescence in patients with age-related maculopathy. *Invest Ophthalmol Vis Sci*. 2004; 45(2):574-583.

17. Csaky KG, Patel PJ, Sepah YJ, et al. Microperimetry for geographic atrophy secondary to age-related macular degeneration. *Surv Ophthalmol*. 2019; 64(3):353-364.

18. Jackson GR, Scott IU, Kim IK, Quillen DA, Iannaccone A, Edwards JG. Diagnostic sensitivity and specificity of dark adaptometry for detection of age-related macular degeneration. *Invest Ophthalmol Vis Sci*. 2014; 55(3):1427-1431.

19. Steinmetz RL, Haimovici R, Jubb C, Fitzke FW, Bird AC. Symptomatic abnormalities of dark adaptation in patients with age-related Bruch's membrane change. *Br J Ophthalmol*. 1993; 77(9):549-554.

20. Curcio CA, Owsley C. Rod-mediated dark adaptation as a suitable outcome for early and intermediate age-related macular degeneration. *Ophthalmology* 2019; 126(6):866-867.

21. Chen KG, Alvarez JA, Yazdanie M, et al. Longitudinal study of dark adaptation as a functional outcome measure for age-related macular degeneration. *Ophthalmology* 2019; 126(6):856-865.

22. Ou WC, Lesmes LA, Christie AH, Denlar RA, Csaky KG. Normal- and low-luminance automated quantitative contrast sensitivity assessment in eyes with age-related macular degeneration. *Am J Ophthalmol*. 2021; 226:148-155.

New Treatments for Dry AMD

Peter K Kaiser MD

I. Reduce Toxic Byproduct Accumulation
   A. Topical GAL-101 (Galimedix)
   B. Oral ALZ-507 (Alzheon)
   C. Intravitreal Fab vs. Ab40 (Boehringer Ingelheim)
   D. Oral RT011 (Retrotope): reduce DHA peroxidation

II. Reduce Oxidative Stress
   A. Elamipretide (Stealth BioTherapeutics)
   B. Risuteganib (Allegro)
   C. Photobiomodulation (LumiThera)
   D. Bioelectric therapy (Biovisics Medical)

III. Visual Cycle Modulators
   ALK-001 (Alkeus)

IV. Stem Cells
   A. Human embryonic stem cells (hESCs)
      1. MA09-hRPE (Astellas)
      2. OpRegen (Lineage Cell Therapeutics)
      3. CPCB-RPE1 (Regenerative Patch Technologies)
      4. HLS001 (Dainippon Sumitomo Pharma)
      5. Retinal pigment epithelium on a membrane (Pfizer)
   B. Human retinal progenitor cells (trophic mechanism)
      1. Intravitreal jCells (jCyte)
      2. Subretinal ReNeuron
      3. Intravitreal CD34+ cells (UCD)

V. HtrA1 Inhibition
   A. RG6147 (Roche)
   B. IC-500 (IvericBio)

VI. NLRP3 Inflammasome Inhibition
   A. Kamuvudine (Inflammasome Therapeutics)
   B. Oral Xiflam (OcuNexus Therapeutics)

VII. Optogenetics
   A. GS030 (GenSight)
   B. BS01 (Bioinc Sight/AGTC)
   C. MCO-010/020 (Nanoscope Therapeutics)
   D. VedereBio/Novartis
   E. Ray Therapeutics

VIII. Complement Modulation (see Figure 1)

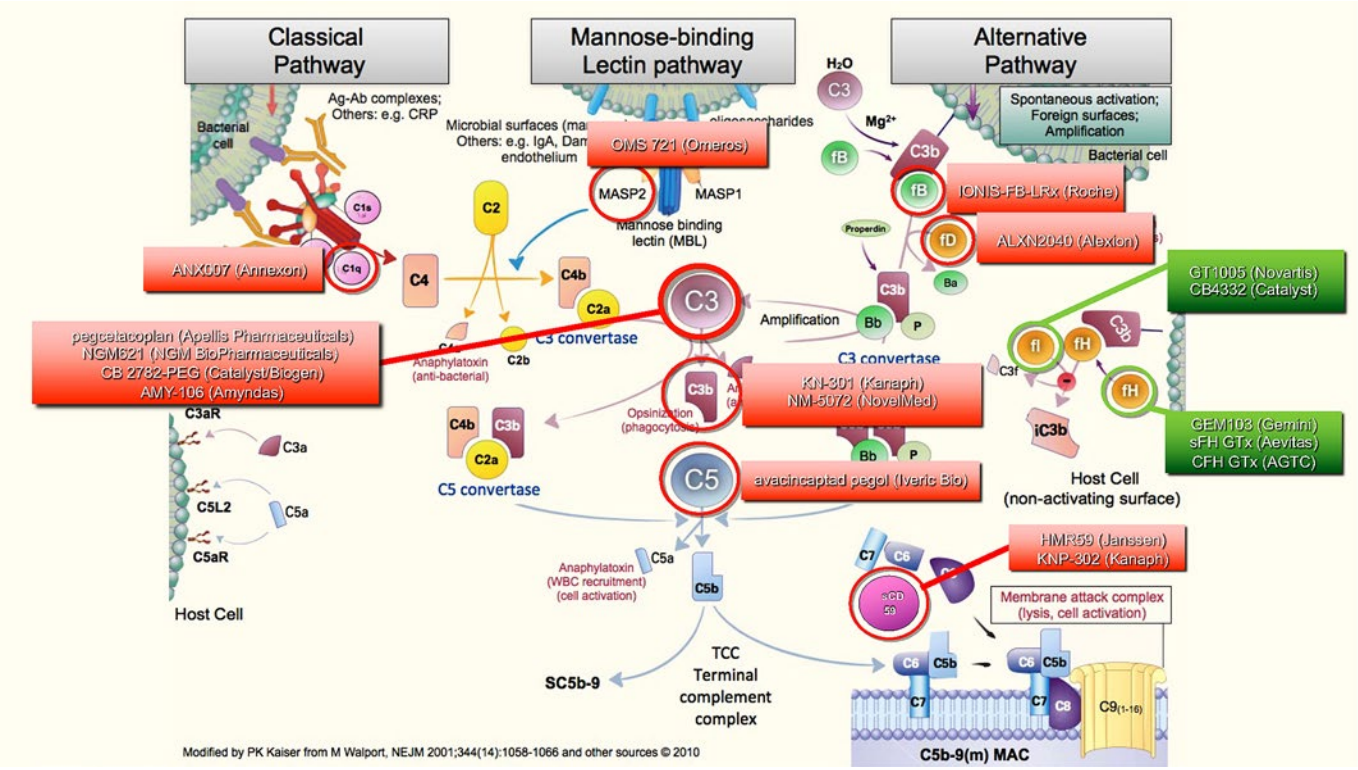

Figure 1

Developing Systemic Biomarkers for AMD

Joan W Miller MD, Inês Laíns MD PhD, and Deeba Husain MD

I. Definition of Biomarkers

II. Identification and Development of AMD Biomarkers

Previously studied serologic biomarkers had inconsistent results.

A. C-reactive protein

B. Oxidative stress and homocysteine

C. HDL, LDL, and triglycerides

D. Others

III. 'Omics as Tools to Characterize and Quantify Biological Molecules That Translate Into Structure and Function

IV. Definition of Metabolomics and Potential as a Tool for Identification of Biomarkers

A. Global profiling of all metabolites: small, low molecular weight molecules (<1-1.5 kDa)

B. Downstream of all genetic transcriptional processes and interactions with environmental exposures

C. Represents functional state and disease phenotype in multifactorial diseases, such as AMD

V. Analytical Tools for Metabolomic Profiling

A. Nuclear magnetic resonance (NMR) spectrometry and mass spectrometry (mass spec)

B. Untargeted metabolomics vs. targeted metabolomics

VI. Sample Types for Metabolomic Analysis

VII. Plasma Metabolites Differ Between Patients With AMD and Controls and Across Different Stages of AMD

A. Most significant metabolites belong to lipid and amino acid pathways.

1. Glycerophospholipids
2. Other lipids belonging to VLDL and HDL classes
3. Glutamate and glutamine
4. Other amino acids (phenylalanine, tyrosine, leucine, and isoleucine)
5. Others (example fatty acids)

B. Several studies focused in neovascular AMD

1. Most showing dysregulation in amino acids (example tyrosine) and carnitine/acylcarnitine
2. Study also in aqueous humor also showing dysregulations in carnitine

VIII. Metabolomic-genomic association showed that lipid metabolism appears to be important in AMD.

A. Most SNPs located in or near genes involved in lipid metabolism (*LIPC*, *ABCA1*, *CETP*, *and APOE*)

B. Most metabolites from lipid pathways: glycerophospholipids, HDL, and VLDL subclasses

IX. Metabolomic Profiles and AMD Progression

To date, only small study with 3 years follow-up

A. Lipid and amino acid metabolites linked to AMD progression (alanine, aspartate, and pathways as well as metabolites linked to oxidative stress)

B. Larger studies with longer follow-up needed to address potential of biomarkers of progression

X. Urine metabolomics are less useful than plasma in AMD.

A. No urinary metabolites identified as differing between patients with AMD and controls

B. Few urinary metabolites shown to differ across stages of disease (but in agreement with plasma)

C. Limitations in measuring lipids

XI. Imaging Metabolomics

A. Currently, AMD classifications are based on color fundus photographs, which have limitations in the assessment of AMD phenotypes.

B. Data supports specific associations between metabolites and OCT features (hyperreflective foci, ellipsoid zone disruption, and atrophy).

XII. Conclusions

A. Need to develop accessible AMD biomarkers and better understand the pathophysiology of different AMD phenotypes

B. Consistent differences identified in plasma metabolomic profile of patients with AMD compared to controls and across stages of disease

1. Glycerophospholipids, HDL and VLDL, and glutamate/glutamine pathway metabolites appear to have the greatest potential as biomarkers for AMD.

2. Targeted studies are needed to further validate these findings.

a. Metabolomic-genomic studies also point to important dysregulations in lipid metabolites in AMD and provide important information to understand the pathophysiology of this disease.

b. Need to assess potential of metabolomics to identify biomarkers of AMD progression and specificities of different OCT/ imaging phenotypes

References

1. Laíns I, Gantner M, Murinello S, et al. Metabolomics in the study of retinal health and disease. *Prog Retin Eye Res*. 2019; 69:57-79.

2. Colijn JM, den Hollander AI, Demirkan A, et al; European Eye Epidemiology Consortium, EYE-RISK Consortium. Increased high-density lipoprotein levels associated with age-related macular degeneration: evidence from the EYE-RISK and European Eye Epidemiology Consortia. *Ophthalmology* 2019; 126(3):393-406.

3. Laíns I, Kelly RS, Miller JB, et al. Human plasma metabolomics study across all stages of age-related macular degeneration identifies potential lipid biomarkers. *Ophthalmology* 2018; 125(2):245-254.

4. Laíns I, Chung W, Kelly RS, et al. Human plasma metabolomics in age-related macular degeneration: meta-analysis of two cohorts. *Metabolites* 2019; 9(7):127.

5. Laíns I, Zhu S, Han X, et al. Genomic-metabolomic associations support the role of LIPC and glycerophospholipids in age-related macular degeneration. *Ophthalmol Sci*. 202; 1(1):100017.

6. Acar IE, Lores-Motta L, Colijn JM, et al; EYE-RISK consortium. Integrating metabolomics, genomics and disease pathways in age-related macular degeneration. *Ophthalmology* 2020; 127:1693-1709.

7. Laíns I, Mendez K, Nigalye A, et al. Plasma metabolomic profiles associated with three-year progression of age-related macular degeneration. *Metabolites* 2022; 12(1):32.

8. Kersten E, Dammeier S, Ajana S, et al. Metabolomics in serum of patients with non-advanced age-related macular degeneration reveals aberrations in the glutamine pathway. *PLoS One*. 2019; 14(6):e0218457.

9. Chao de la Barca JM, Rondet-Courbis B, Ferré M, et al. A plasma metabolomics profiling of exudative age-related macular degeneration showing carnosine and mitochondrial deficiencies. *J Clin Med*. 2020; 9(3):631.

10. Laíns I, Mendez KM, Gil JQ, et al. Urinary mass spectrometry profiles in age-related macular degeneration. *J Clin Med*. 2022; 11(4):940.

Surgical Management of Retinal Detachment After Open Globe Injury

Dean Eliott MD

I. Incidence of Retinal Detachment After Open Globe Injury

Based on 10-year review of ~900 open globe cases[1]

A. 8% at presentation and within 1 day after presentation

B. 13% at presentation and within 1 week after presentation

C. 21% at presentation and within 1 month after presentation

D. 29% at presentation and within several years after presentation

II. Risk Factors for Retinal Detachment After Open Globe Injury

Probability of developing retinal detachment can be predicted using open globe injury score based on the following risk factors:[1,2]

A. Visual acuity at presentation

B. Zone of injury

C. Vitreous hemorrhage

III. Indications for Vitrectomy After Open Globe Injury

Based on >60 eyes with open globe injury that underwent vitrectomy[3]

A. Retinal detachment (without retinal incarceration in wound) comprised 39% of cases.

B. Media opacity comprised 28% of cases.

C. Retinal incarceration in wound (± retinal detachment) comprised 13% of cases.

D. Progressive vitreoretinal traction comprised 11% of cases.

E. Intraocular foreign body comprised 5% of cases.

F. Endophthalmitis comprised 3% of cases.

IV. Comorbidities Noted During Vitrectomy for Open Globe Injury

Based on >60 eyes with open globe injury that underwent vitrectomy[3]

A. Iris trauma in 62% of cases

B. Lens expulsion in 54% of cases

C. Subretinal hemorrhage in 51% of cases

D. Hyphema in 41% of cases

E. Choroidal hemorrhage in 30% of cases

F. Corneal trauma in 20% of cases

V. Secondary Procedures Performed After Primary Repair of Open Globe Injury

A. Indications

1. Media opacity
2. Progressive vitreoretinal traction (± retinal detachment)
3. Retinal incarceration in wound (± retinal detachment)
4. Retinal detachment

B. Timing: typically 7-14 days after primary repair surgery

1. Less bleeding
2. Easier to create posterior vitreous detachment (PVD)

C. Goals of vitrectomy

1. Create PVD
2. Relieve vitreous traction
3. Relieve retinal traction (in cases with incarceration and/or proliferative vitreoretinopathy, PVR)
4. Reattach retina (using variety of techniques, which may include membrane peeling, scleral buckle, retinectomy, perfluorocarbon liquid, endolaser, extended tamponade)

VI. Surgical Technique

Retinectomy is commonly used for retinal incarceration and/or PVR. General principles of retinectomy for retinal detachment after open globe injury:[5]

A. Strongly consider lensectomy in phakic eyes (lower incidence of hypotony with aphakia).

B. Consider scleral buckle to support vitreous base (except in cases with 360-degree retinectomy).

C. Retinectomy performed after attempted complete epiretinal membrane removal: if retinectomy is done before complete epiretinal membrane removal, further membrane removal may be difficult.

D. Orientation: circumferential, posterior to vitreous base

E. Location

1. Avoid retinectomy edge near 6 o'clock position.
2. Most common retinectomy location is inferiorly with edges at 3 o'clock and 9 o'clock.

F. Size

1. Retinectomy should extend into normal retina surrounding areas of traction.
2. Most common retinectomy size is 6 clock hours or 180 degrees.
3. If greater than 270 degrees, extend the retinectomy to 360 degrees.

G. Hemostasis: diathermy used to delineate intended edge and to prevent intraoperative bleeding

H. Instruments: vitrectomy probe (or scissors) used to cut retina

I. Adjuvants: May consider perfluorocarbon liquid to stabilize posterior retina

J. Complete excision of anterior retina to prevent postoperative proliferation with resultant traction on the retinectomy edge or ciliary body (lower incidence of hypotony with removal of anterior retina)

K. Retinopexy: confluent endolaser to the retinectomy edge ± 360-degree endolaser

L. Extended tamponade: C_3F_8 gas or silicone oil

1. Silicone Oil Study showed equal efficacy in eyes with retinectomy.
2. Recent studies favor silicone oil over gas; redetachment occurs in 4%-25% after oil removal.[6]

VII. Recurrent Retinal Detachment due to PVR After Open Globe Injury

A. Risk factors

1. Smoking[4]
2. Presence of PVR at time of initial retinal detachment repair[3,4]
3. Subretinal hemorrhage noted at time of initial vitrectomy[3]
4. Absence of scleral buckle performed during initial vitrectomy[4]
5. Retinectomy performed during initial vitrectomy[3]

B. Incidence: ~50%[3,4]

C. Outcomes

1. After initial retinal detachment repair:[3] 100% reattached intraoperatively (many with large retinectomies)
2. After initial retinal detachment repair ± reoperations for recurrent detachment due to PVR[3]
   a. 80% completely attached at last follow-up.
   b. 14% partially attached at last follow-up.
   c. 6% remained detached at last follow-up.

References

1. Stryjewski TP, Andreoli CM, Eliott D. Retinal detachment after open globe injury. *Ophthalmology* 2014; 121(1):327-333.
2. Brodowska K, Stryjewski TP, Papavasileiou E, Chee YE, Eliott D. Validation of the retinal detachment after open globe injury (RD-OGI) score as an effective tool for predicting retinal detachment. *Ophthalmology* 2017; 124(5):674-678.
3. Ung C, Stryjewski TP, Eliott D. Indications, findings, and outcomes of pars plana vitrectomy after open globe injury. *Ophthalmol Retina*. 2020; 4(2):216-223.
4. Eliott D, Stryjewski TP, Andreoli MT, Andreoli CM. Smoking is a risk factor for proliferative vitreoretinopathy after traumatic retinal detachment. *Retina* 2016; (0):1-7.
5. Abrams GW, Garcia-Valenzuela E, Nanda SK. Retinotomies and retinectomies. In: Ryan SJ, ed. *Retina*, 3rd ed. CV Mosby; 2000:2311-2343.
6. 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.

Small Uveal Melanoma: The Role of the Vitreoretinal Surgeon

Timothy G Murray MD MBA

Overview

- Primary and secondary management of small uveal melanoma hold the greatest promise to reduce melanoma-related mortality.
- Traditional approaches have focused on radiotherapy (brachytherapy or charged particle) or enucleation, neither of which is appealing in the primary management of small uveal melanoma.
- Traditionally, concerns with diagnostic accuracy and treatment efficacy slowed the adoption of early treatment as a viable strategy compared with delayed treatment (observation).
- Uveal melanoma remains a clinical diagnosis and requires expertise in evaluation to ensure diagnostic accuracy.
- Major findings for transition to malignancy include growth, orange pigment, subretinal fluid, initial size, location, symptoms, and atypical internal echographic reflectivity.

Approach

- Once established, the diagnosis of small uveal melanoma typically requires definitive therapy to minimize/eliminate metastatic risk.
- Advances in biopsy for genetic prognostication now play a major role in tumor management.
- The most controlled approach to biopsy utilizes small-gauge microincisional valved vitrectomy (MIVS) with fluidic control, best approached via 3-port vitrectomy and wide-field viewing.
- MIVS as a primary treatment strategy for small uveal melanoma has now been reported with over 5 years of follow-up in a large consecutive series.
- Technically, the approach incorporates small-gauge vitrectomy with valved fluidics, removal of vitreo-tumoral traction, removal of macular internal limiting membrane, confluent endolaser tumor ablation, 25-gauge multipass fine needle aspiration biopsy for gene expression profiling (GEP), and intravitreal triamcinolone acetonide to modulate post-treatment inflammation. Each of these steps has proven critical to excellent tumor control with minimized morbidity.

Results

- Local tumor control: approximately 99% at 5 years
- GEP biopsy positive results approaching 98%
- Post-treatment progressive retinal detachment: 1%-2%
- Melanoma-associated metastatic disease: less than 1% at 5 years
- Enucleation rates: None
- Endophthalmitis rates: None
- Intraocular tumor dissemination: None

Discussion

Advances in vitreoretinal surgery have now enabled a targeted microsurgical approach to small tumor management that enhances precision tumor treatment, incorporates advanced biopsy techniques, exhibits excellent tumor control, and minimizes treatment-related morbidity. Continued focus on enhanced strategies for small tumor melanoma management remain the single best approach to reduce melanoma-related mortality.

The Role of Vitreoretinal Surgical Techniques in the Management of Uveal Melanoma

Tara A McCannel MD PhD

I. Introduction
   A. Controversy
      1. Fear of manipulation causing tumor seeding and metastasis
      2. Lack of vitreoretinal training in most ocular oncologists
      3. Ocular oncologists slow to adopt novel approaches
      4. Few centers with experience combining vitreoretinal approaches with tumor management
   B. Critical for modern approaches to visual preservation
      1. Traditional approach to uveal melanoma is focused on tumor control.
      2. Preserving vision is not part of management strategy at most centers.

II. Radiation Shielding
   A. Role of silicone oil
      1. Rationale, data supporting improved vision
      2. Palladium-103 is better shielded than iodine-125; move to palladium-103 as primary radioisotope
   B. Future materials for radiation shielding

III. Management of Retinal Detachment
   A. Serous retinal detachment
      1. Frequently left for "observation only"
      2. Vitrectomy is only path for improving vision.
   B. Rhegmatogenous retinal detachment: Abnormal RPE-choroid requiring different surgical approaches

IV. Management of Vitreoretinal Comorbidities: Macular Pucker and Holes
   A. Frequently left for "observation only"
   B. Vitrectomy required for visual improvement

V. Summary

Current Concepts in Macular Hole Surgery

Sophie J Bakri MD

NOTES

Advances in Technology and Imaging in Vitreoretinal Surgery

David R Chow MD

NOTES

Surgical Videos—Cool Cases and Complications

Kourous Rezaei MD

Failed Large Macular Hole

Tongalp H Tezel MD

Subretinal Silicone Oil

Ehab N El Rayes MD PhD

Retinal Detachment in Osteodentokerathoprosthesis

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Intraocular Foreign Body

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None

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Everads Therapy, Ltd.: C
EyePoint Pharmaceuticals: C
Foresight Biotherapeutics: C
Galimedix Therapeutics: C
Genentech: C
GenSight Biologics: C
Glaukos Corp.: C
Glaukos: C
GrayBug Vision: C
Iconic Therapeutics: C
InflammX: C,SO
Interface Biologics, Inc.: C
Ionis: C
Iveric: C
Kala Pharmaceuticals: C
LumiThera, Inc.: C
Nanoscope: C
Neurotech: C
NGM Biopharma: C
Notal Vision, Inc.: C
Novartis Pharma AG: C
Novartis Pharmaceuticals Corp.: C
Novartis, Alcon Pharmaceuticals: C,S
Ocugen, Inc.: C,SO
Ocular Therapeutics: C
Ocular Therapeutix: C,S
Ocuphire: C
Opthea: C
Optos, Inc.: C
Optovue: C
Ora, Inc.: C
Orbit Biomedical: C
Oxurion: C
RecensMedical, Inc.: C
Regeneron Pharmaceuticals, Inc.: C
Regenix-Bio: C
Regenxbio: C
Regulus Therapeutics: C
River Vision: C
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Santen, Inc.: C
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Taiwan Liposomal Company: C
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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, Inc.: C
Bayer Healthcare Pharmaceuticals: S
Biocon: S
Biogen, Inc.: S
Boehringher Ingleheim: S
Eye Point: S
Genentech: S
Merck & Co., Inc.: 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 Pharmaceuticals, Inc.: 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
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 Company: S
ThromboGenics, Inc.: C,S
Tyrogenix: C,S
Vinci: C

Peter A Campochiaro MD
Allegro: SO
AsclipiX: C,S
Ashvattha Therapeutics: C,S
Bausch + Lomb: C
Catawba Research: C
Celanese: C
Clearside: C
Cove Therapeutics: PS
ExgenesisBio: C,S
Exonate: C
Genentech: C,S
Genzyme: S
Graybug Vision: SO
Gyroscope: C
Intrexon: C
Mallinckrodt Pharmaceuticals: S
Merck & Co., Inc.: C
Novartis, Alcon Pharmaceuticals: C
Oxford BioMedica: S
Perfuse: C
Regeneron: C,S
RegenX Bio: S
Roche: C,S
Wave Life Sciences: C

Antonio Capone Jr MD
Aura Biosciences: S
Caeregen: P,PS
Genentech: S,C
Ionis Pharmaceuticals, Inc.: S
Iveric: S
NeoLight: P,PS
Novartis Pharmaceuticals Corp.: S
ProQR Therapeutics: C
Regeneron Pharmaceuticals, Inc.: S
Regeneron: S
Spark Therapeutics: C

Usha Chakravarthy MBBS PhD
AbbVie: C
Adverum: C
Alimera Sciences, Inc.: C
Alnylam Pharmaceuticals: C
Apellis Pharmaceuticals, Inc.: C
Boehringer Ingelheim: C
DeepEye: C
Isarna: C
RetinaAI: C
Roche Diagnostics: C
Unity: C

R V Paul Chan MD
Alcon Laboratories, Inc.: C
NeoLight: C
Siloam Vision: EO

Stanley Chang MD
Alcon Laboratories, Inc.: L
Genentech: C

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

Gemmy Chui Ming Cheung MB BChir FRCOphth
Allergan: L
Bayer Healthcare Pharmaceuticals: C,L,S
Boehringer-Ingelheim: C,S
Carl Zeiss Meditec: S
Novartis, Alcon Pharmaceuticals: C,L,S
Roche Diagnostics: C
Topcon Medical Systems Inc.: S

Jay K Chhablani MBBS
AbbVie: L
Allergan, Inc.: L
Novartis Pharma AG: C
Salutaris: C

Michael F Chiang MD
Genentech: S
Novartis Pharmaceuticals Corp.: C

David R Chow MD
Alcon Laboratories, Inc.: C
Allergan: C
Bayer Healthcare Pharmaceuticals: C,L
DORC International, bv/Dutch Ophthalmic, USA: C
DORC: L
Novartis, Alcon Pharmaceuticals: C,L
Optovue: L
Roche Diagnostics: C

Carl C Claes MD
Alcon Laboratories, Inc.: C

Michael Nathan Cohen, MD
Alimera Sciences, Inc.: C
Allergan, Inc.: C
Keeler Instruments, Inc.: C

Karl G Csaky MD
AbbVie: C
Adverum Biotechnologies: C
Allergan: C
Annexon Biosciences: C,S
EyeBio: C
Genentech/Roche: C,S
Gyroscope: S
Heidelberg Engineering: C
Johnson & Johnson: C
Merck & Co., Inc.: C
NGM Biopharmaceuticals: C,S
Novartis Pharma AG: C,S
Ocular Therapeutix: C
ReNeuron: C
Retrotope: C
Ribomic: C

Catherine A Cukras MD PhD
Has not disclosed to date

Hakan Demirci MD
Castle Biosciences: C

Dilsher S Dhoot MD
Alimera Sciences, Inc.: C
Allergan: C
Apellis Pharmaceuticals, Inc.: 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
Boerhinger Ingelheim: C,S
Eyepoint: C
Genentech: C
Kodiak Sciences: C,US
Mallinckrodt Pharmaceuticals: C
Novartis Pharma AG: C,S
Regeneron Pharmaceuticals, Inc.: C,S
Santen, Inc.: C,S

Kimberly A Drenser MD PhD
Caeregen Therapeutics: EO
Neolight: PS
Regeneron Pharmaceuticals, Inc.: C
Spark Therapeutics, Inc.: C

Jay S Duker MD
Aura Bio: I
EyePoint Pharma: EE,SO,US
Hubble Therapeutics: C
Sesen Bio: C,SO,US

Jacque L Duncan MD
AbbVie: S
Acucela, Inc.: S
AGTC: C
Biogen, Inc.: S
Cone Sight: C
DTx Therapeutics: C
Editas: C
Eyevensys: C
Gyroscope: C
Helios: C
Nacuity: C
ProQR Therapeutics: C
PYC Therapeutics: C
SparingVision: C
Spark Therapeutics, Inc.: C
Vedere Bio: C

Justis P Ehlers MD
Adverum: C,S
Aerpio: C,S
Alcon Laboratories, Inc.: C,S
Allegro: C
Allergan: C,S
Apellis Pharmaceuticals, Inc.: C
Bioptigen: P
Carl Zeiss Meditec: S,C
Genentech: C,S
Iveric Bio: C,S
Leica: P
Novartis Pharma AG: C,S
Regeneron Pharmaceuticals, Inc.: C,S
Regenxbio: C
Roche: C,S
Stealth: C,S
Thrombogenics: C,S

Ehab N El Rayes MD PhD
None

Dean Eliott MD
Alcon Laboratories, Inc.: C
Alderya Therapeutics, Inc.: C,P,US
Allergan, Inc.: C
Asclepix: C
Cocoon Biotechnology: C,SO
DORC: C
Genentech: C
Neurotech: S
Pykus Therapeutics: C,PS
Unity Biotechnology: S

Amani Fawzi MD
Boehringer Ingelheim, Inc.: S
Boehringer Ingelheim: C
Medical Conference Planning International: L
Novartis Pharma AG: C
Regeneron Pharmaceuticals, Inc.: C
Roche, Inc.: C

Philip J Ferrone MD
Allergan, Inc.: C
Apellis Pharmaceuticals, Inc.: C,S
ArcticDx: PS,SO
Genentech: C,S
Gyroscope: S
Regeneron Pharmaceuticals, Inc.: S

Marta Figueroa MD
Alcon Laboratories, Inc.: C
Allergan, Inc.: C
Bayer Healthcare Pharmaceuticals: C
Novartis Pharma AG: C
Orbit Biomedical Inc.: C
Roche: C
Zeiss: C

Harry W Flynn Jr MD
None

James C Folk MD
None

Jasmine H Francis MD
None

K Bailey Freund MD
Allergan: C
Bayer Healthcare Pharmaceuticals: C
Genentech: C,S
Heidelberg Engineering: C
Novartis, Alcon Pharmaceuticals: C
Regeneron Pharmaceuticals, Inc.: C
Zeiss: C

Sunir J Garg MD FACS
Allergan, Inc.: C
American Academy of Ophthalmology: C
Apellis Pharmaceuticals, Inc.: S
Bausch + Lomb: C
Boehringer Ingelheim: C,S
Coherus: C
Johnson & Johnson: C
Kodiak: S
Merck Manual: C
NGM Bio: S
Regeneron Pharmaceuticals, Inc.: S

Alain Gaudric MD
None

Debra A Goldstein MD
AbbVie: C
Allergan: C
Bausch + Lomb: C

Evangelos S Gragoudas MD
Astellas Institute for Regenerative Medicine: C
Aura Pharmaceuticals: C
Valeant: P

John Grigg, MBBS
Belitebio: C

J William Harbour MD
Castle Biosciences, Inc.: C
Immunocore, Ltd.: C

Mary Elizabeth Hartnett MD FACS
Knights Templar Eye Foundation, Inc.: C
Lippincott Williams & Wilkins: P
NIH/NEI: S
Novartis: S
Parexel: S
Regeneron Pharmaceuticals, Inc.: C

Sohail J Hasan MD PhD
None

Tarek S Hassan MD
Alcon Laboratories, Inc.: C
Allergan: C
Apellis Pharmaceuticals, Inc.: C
Aviceda Therapeutics: EE,PS
Bayer Healthcare Pharmaceuticals: C
Beaver-Visitec International, Inc.: C
Carl Zeiss Meditec: C
Genentech: C
Hoffman La Roche, Ltd.: C
ImprimisRx: C
Iveric Bio: C
Katalyst Surgical, LLC: C,P
Novartis Pharmaceuticals Corp.: C
Ocugenix: C
Oculus Surgical, Inc.: C,P
Ocutrx: C
Springtail Technologies: EO,PS,US
Surgicube: C
Vitreq: C

Jeffrey S Heier MD
4DMT: C
BVT: C
2020 Onsite: C
Abpro: C
Adverum: C,US
Affamed: C
Alderya Therapeutics, Inc.: US
Allegro: C
Allergan: C
Annexon: C,S
Apellis Pharmaceuticals, Inc.: C,S
Asclepix: C,S
Aviceda: C,SO
Bayer: S
Biovisics: C
DTx: C,SO
Gemini Therapeutics: C
Genentech/Roche: C,S
Graybug: C
Gyroscope: C,S,SO
Iveric: C,S
jCyte: C,PS
Johnson & Johnson Vision: C,S
Kanghong: C,S
Kodiak: S
Nanoscope: C
NGM: C,S
Notal Vision: C,S
Novartis: C,S
Ocular Therapeutix: C,US
OcuTerra: C
Oxurion: C
Palatin: C
Perceive Biotherapeutics: C
Regeneron: C,S
Regenxbio: C,S
RevOpsis: C,PS
Stealth Biotherapeutics: C,S
Surrozen: C
Thea: C
Unity Biotherapeutics: C
Verseon: C
Vinci: C,PS

Allen C Ho MD
AcuSurgical: C
Adverum: C,S
Aerie Pharmaceuticals, Inc.: C,S
AGTC: C,S
Alcon Laboratories, Inc.: C,S
Alderya Therapeutics, Inc.: C,S
Allergan: C,S
Apellis Pharmaceuticals, Inc.: S,C
Asclepix: C,S
Atsena: C,S
Beaver-Visitec International, Inc.: C
Chengdu Kanghong Biotechnology: C,S
Clearside Biomedical: C
Covalent Medical, LLC: PS
Dompe: C
Eyevensys: C
Genentech: C,S
Graybug: C
Gyroscope: C,US,S
Iconic: C,S
Iridex: C,S
Iveric: C,S
Johnson & Johnson: C,S
Kiora: C,US
Lineage/BioTime: C,S
Lumithera: S
Notal: C,S
Novartis: S
Ocular Therapeutics: C
ONL: C,PS
Oxular: C
ProQR: S
Regeneron Pharmaceuticals, Inc.: C,S
Regenexbio: C,S
Vanotech: C

Nancy M Holekamp MD
Allergan, Inc.: C,L
Annexon: C
Apellis Pharmaceuticals, Inc.: C
Bayer: C,L
Cardinal: C
Clearside: C
EyePoint Pharmaceuticals: C
Gemini: C,S
Genentech: C,L,S
Gyroscope: S
Nacuity: C
NGM Therapeutics: C
Notal Vision: C
Regeneron Pharmaceuticals, Inc.: C,L
Spark: L
Stealth Biosciences: C
Thea Laboratoires: C

Suber S Huang MD MBA
Lumithera/Diopsys: C,L,SO
Lumoptik: US,C
Nidek, Inc.: C
Outlook Therapeutics: C
Regenerative Patch Technologies: C
Regenxbio: C
Second Sight Medical Products: C
Volk Optical, Inc.: C,L

G Baker Hubbard MD
None

Jean-Pierre Hubschman MD
Alcon Laboratories, Inc.: C
Allergan: C
Bausch + Lomb: C
Horizon Surgical: EO,EE

Mark S Humayun MD PhD
Alcon Laboratories, Inc.: C,L
Duke Eye Center: P
Golden Eye/Intellimicro: P,PS
Iridex: P
John Hopkins University: P
Lutronic Vision: C,SO
Outlook Therapeutics: SO,US
Regenerative Patch Technologies: C,P,PS
Replenish: C,P,PS
Second Sight Medical Products, Inc.: P

Raymond Iezzi MD
None

Michael S Ip MD
Alimera Sciences, Inc.: C
Allergan, Inc.: C
Amgen Inc.: C
Biogen: C
Cell Lineage Therapeutics: C
Clearside: C
Genentech: C
Iveric Bio: C
Novartis Pharma AG: C
Occurx: C
Regeneron Pharmaceuticals, Inc.: C
Regenexbio: C

Douglas A Jabs MD MBA
None

Glenn J Jaffe MD
Adverum: C
Annexon: C
EyePoint: C
Hoffman La Roche, Ltd.: C
Iveric: C
Neurotech: C
Novartis Pharma AG: C
Oxurion: C

Chirag D Jhaveri MD
Boehringer-Ingelheim: C,S
DRCR Retina Network: S
Genentech: C,S
Gyroscope Therapeutics: S
Kodiak Sciences: S
Novartis: S
Opthea: S
Oxurion: S
Regenxbio: S,C

Mark W Johnson MD
Amgen, Inc.: C
Apellis Pharmaceuticals, Inc.: S
Aura Biosciences: C

Peter K Kaiser MD
Aerie Pharmaceuticals, Inc.: 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
jCyte: C
Kala Pharmaceuticals, Inc.: C
Kodiak: C
Novartis Pharmaceuticals Corp.: C,L
Omeros: C
Oxurion: C
Regeneron Pharmaceuticals, Inc.: C,L
RegenexBio: C
Stealth: C

Richard S Kaiser MD
None

Christine Nichols Kay MD
4D Therapeutics: S
AGTC: C,S
Alkeus: S
Atsena Therapeutics: C,SO
Biogen Inc: S
Gyroscope: S
Iveric Bio: S
Kiora: C,SO
Kodiak: S
MeiraGTx: S
Novartis Pharma AG: C
Opus: C
ProQR: S
Regenxbio: S
Spark Therapeutics, Inc.: C

Peter J Kertes MD
Allergan: C
Bayer Healthcare Pharmaceuticals: C,L,S
Genentech: S
Novartis, Alcon Pharmaceuticals: C,L,S;
Novelty Nobility: C
Pfizer, Inc.: L
Roche: C,S
Zeiss: L

Arshad M Khanani MD
Adverum: C,S
Alkahest: S
Allergan: C,L,S
Gemini: C,S
Genentech: C,S
Graybug: C,S
Gyroscope: C,S
Iveric Bio: C,S
Kato Pharmaceuticals, Inc.: C
Kodiak Sciences: C,S
Neurotech: S
NGM Pharmaceuticals: S
Novartis Pharmaceuticals Corp.: 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
Kodiak Sciences: C
Novartis: C

Judy E Kim MD
Alimera Sciences, Inc.: C
Allergan: C
Astellas: C
DORC: C
Genentech: C
Notal Vision, Inc.: S
Novartis: C
Optos, Inc.: S
Regeneron: C

Baruch D Kuppermann MD PhD
Allegro Ophthalmics, LLC: C,S,SO
Allergan: C,L,S
EyeBio: C,SO
Eyedaptic: C,SO
Genentech, Inc.: C,S
Glaukos Corp.: C
Interface Biologics: C
Ionis: S
Iveric Bio: C,S
jCyte: C,SO
Novartis Pharmaceuticals Corp.: C,S
Regeneron Pharmaceuticals, Inc.: C,S
ReVana Therapeutics: C,SO
Ripple Therapeutics: C
Theravance Biopharma: C

Eleonora G Lad MD PhD
Alexion: C
Annexon: C
Apellis Pharmaceuticals, Inc.: C
Hoffman La Roche, Ltd.: S
Hoffmann La Roche: C
Iveric Bio: C
Janssen: C
NGM Biotherapeutics: C
Novartis, Alcon Pharmaceuticals: S
Retrotope: C
Thea Laboratoires: C

Paolo Lanzetta MD
Abbvie: C
Aerie Pharmaceuticals, Inc.: C
Apellis Pharmaceuticals, Inc.: C
Bausch + Lomb: C
Bayer Healthcare Pharmaceuticals: C,L
Biogen International Gmbh: C
Boerhinger: C
Centervue, Inc.: C
Genentech: C
Novartis Pharma AG: C
Outlook Therapeutics: C
Roche: C

Aaron Y Lee MD
Carl Zeiss Meditec: S
Genentech: C
Gyroscope: C
Johnson & Johnson Vision: C
Santen, Inc.: S
Verana Health: C

Jennifer Irene Lim MD
Adverum Biotechnologies: S
Alderya Therapeutics, Inc.: S
Allergan, Inc.: C
Aura Biosciences: C
Chengdu Kanghong: S
Cognition Therapeutics: C
CRC Press/Taylor and Francis: P
Eyenuk: C
Genentech: C,S,L
Greybug: S
Iveric Bio: C
Luxa: C
NGM: S
Novartis Pharma AG: C
Opthea: C
Quark: C
Regeneron Pharmaceuticals, Inc.: C,S
Santen, Inc.: C
Stealth: S
Unity: C
Viridian: C

Phoebe Lin MD PhD
Bausch + Lomb: L
Roche Diagnostics: C

Anat Loewenstein MD
Allergan: C
Bayer Healthcare Pharmaceuticals: C
Beyeonics: C
Notal Vision, Inc.: C
Novartis Pharmaceuticals Corp.: C
Roche: C

Mathew W MacCumber MD PhD
Alimera Sciences, Inc.: C,S
Apellis Pharmaceuticals, Inc.: C,S
Bausch + Lomb: C
Cardinal Health: C
Genentech: C
Novartis Pharma AG: C,S
Regeneron: C
RegenxBio: S
Spark Therapeutics: C
US Retina: C,PS

Dennis M Marcus MD
Aiviva: S
Alcon Laboratories, Inc.: S
Alexion: S
Allegro: S
Allergan: S
Amgen, Inc.: S
Annexon: S
Apellis Pharmaceuticals, Inc.: S
Boehringer Ingleheim: S
Chengdhu: S
Clearside: S
Gemini: S
Genentech: C,S
GlaxoSmithKline: S
Graybug: S
GTscope/Gyroscope: S
Ionis: S
Iveric: S
Kalvista: S
Kodiak: S
Mylan: S
Novartis Pharmaceuticals Corp.: S
Oculis: S
Ophthotech: S
Opthea: S
Optos/Nidek: S
Outlook: S
Pfizer, Inc.: S
Regeneron Pharmaceuticals, Inc.: S,C
Regenxbio: C,S
Roche: C,S
Samsung: S
Stealth/Spiam: S
ThromboGenics, Inc.: S
Topcon: S
Xplore: S
Zeiss: S

Daniel F Martin MD
None

Colin A McCannel MD
Alderya Therapeutics, Inc.: S
DORC International, bv/Dutch Ophthalmic, USA: C,L
Genentech: S
Regenexbio, Inc.: S

Tara A McCannel MD
None

Stephen D McLeod MD
Forsight: P

Michel Michaelides MD
2CTech: C
Acucela: C
Stargazer Pharmaceuticals: C

William F Mieler MD
None

Joan W Miller MD
Aptinyx, Inc.: C,US
Ciendias Bio: PS
Genentech/Roche: C
Heidelberg Engineering: C
Kalvista Pharmaceuticals: C
Lowy Medical Research Institute, Ltd.: S
ONL Therapeutics, LLC: C,PS,P
Sunovion: C
Valeant Pharmaceuticals: P

Andrew A Moshfeghi MD MBA
Alimera Sciences, Inc.: C
Allergan, Inc.: C
Genentech: C,S
Graybug: C
Novartis Pharma AG: C,S
Ocular Therapeutix: C,SO
OptiStent: C,PS
Placid0: C,PS
Pr3vent: C,PS
Regeneron Pharmaceuticals, Inc.: C,S
Regenxbio: C
Valitor: C
Waldo: SO,PS,C

Darius M Moshfeghi MD
1800 Contacts: PS
Ainsly, Inc.: PS,C
Akceso Advisors AG: C
Alexion: C
dSentz, Inc.: PS,EO
Genentech: S
M3 Global Research: C
Placid0, Inc.: PS,EO
Pr3vent, Inc.: PS,EO
Prime Medical Education: C
Promisight, Inc.: EO,PS
Pykus: PS
Regeneron Pharmaceuticals, Inc.: C
Versl, Inc.: PS
VRS: L

Prithvi Mruthyunjaya MD
Alcon Laboratories, Inc.: C
Aura: C
Castle Biosciences, Inc.: C
Genentech: C,S

Rajeev H Muni MD
None

Marion Ronit Munk MD PhD
Acucela, Inc.: C
Allergan: L
Bayer: C,S
Gensight Therapeutics: C
Helbling: C
Isarna Therapeutics: C
Lumithera: C
Novartis: C,L
OcuTerra: C
RetinAI: C
Roche: C
Zeiss: C,L

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

Aaron Nagiel MD PhD
Allergan, Inc.: C
Biogen, Inc.: C
CRISPR: US
Homology Medicines: US
MustangBio: US
Novartis Pharma AG: C
PassageBio: US
Regenxbio: C

Melissa D Neuwelt MD
None

Quan Dong Nguyen MD
Bausch + Lomb: C
Genentech: C
Kriya Therapeutics: C
Novartis: C
Regeneron Pharmaceuticals, Inc.: C
Retrotope: C
Rezolute: C
Santen, Inc.: C

Kyoko Ohno-Matsui MD
Cooper Vision: C
Santen, Inc.: C

Ghazala A Datoo O'Keefe MD
None

Timothy W Olsen MD
iMacular Regeneration LLC: P,EO
Novartis Institutes for BioMedical Research, Inc.: S

Sengul C Ozdek MD
Allergan, Inc.: C
Bayer Healthcare Pharmaceuticals: C
Novartis Pharma AG: C
Roche Diagnostics: C

Susanna S Park MD PhD
Allergan: S
Cures Within Reach: S
Department of Defense: I
Greybug Vision: S
National Eye Institute: S,I
Ophthea Ltd.: S
Retina Society: S
Roche: S

Purnima S Patel MD
None

Dante Pieramici MD
4DMT: S
Adverum: C,S
Apellis Pharmaceuticals, Inc.: S
Clearside: S
Gemini: C,S
Genentech: C,S
Greybug: S
Ionis: S
Kodiac: S
NGM: S,C
Novartis Pharma AG: S
Ocular Therapeutic: S
Ophthea: S
Regeneron Pharmaceuticals, Inc.: C,S
Regenxbio: C,S
Stealth: S
Unity: C,S

Pradeep S Prasad MD
Alimera Sciences, Inc.: C;
DORC International, bv/Dutch Ophthalmic, USA: L
OD-OS GmbH: L

Jonathan L Prenner MD
EyeBio: C,SO
Genentech: L

Jose S Pulido MD MS
None

Giuseppe Querques MD
None

Aleksandra V Rachitskaya MD
AGCT: S
Alcon Laboratories, Inc.: C
Apellis Pharmaceuticals, Inc.: L,S
Genentech: C,L,S
NGM Biopharmaceuticals: S
Novartis Pharma AG: C,S
Regeneron: L
Zeiss: C

Carl D Regillo MD FACS
Adverum: C,S
Alcon Laboratories, Inc.: C,S
Allergan: C,S
Apellis Pharmaceuticals, Inc.: C,S
Clearside: C,S
Eyepoint: C,S
Genentech: C,S
Iveric: C,S,US
Kodiak: C,S
Merck & Co., Inc.: C
Notal Vision, Inc.: C
Novartis Pharmaceuticals Corp.: C,S
Regeneron Pharmaceuticals, Inc.: S
Regenxbio: C,S

Kourous Rezaei MD
Alcon Laboratories, Inc.: C
BMC: C
Iveric Bio (till Dec 2020): EE,US
Iveric Bio (till July 2021): C,SO

Stanislao Rizzo MD
None

Richard B Rosen MD
Astellas: C
Boehringer Ingelheim: C
CellView: C,PS
Genentech: S
Guardion Health: C,US
Nano Retina: C
Ocusciences: S
OD-OS: C
Opticology: PS
Optovue: C,P,PS
Regeneron Pharmaceuticals, Inc.: C
Topcon Medical Systems, Inc.: S

Philip J Rosenfeld MD PhD
Apellis Pharmaceuticals, Inc.: C,US
Bayer Healthcare Pharmaceuticals: C
Boehringer-Ingelheim: C
Carl Zeiss Meditec: C,S
Chengdu Kanghong Biotech: C
Gyroscope Therapeutics: S
InfllammX Therapeutics: C,SO
Ocudyne: C,SO
Regeneron Pharmaceuticals, Inc.: C
Stealth Biotechnology: S
Unity Biotechnology: C
Valitor, Inc.: C,SO

Srinivas R Sadda MD
4DMT: C
Alexion: C
Allergan: C
Amgen, Inc.: C
Apellis Pharmaceuticals, Inc.: C
Astellas: C
Bayer Healthcare Pharmaceuticals: C
Carl Zeiss Meditec: C,L,S
Centervue: C
Genentech: C
Gyroscope: C
Heidelberg Engineering: C,L,S
Iveric Bio: C
Jannsen: C
Nanoscope: C
Nidek: L
Novartis Pharma AG: C,L
Optos, Inc.: C
Oxurion: C
Pfizer, Inc.: C
Regeneron Pharmaceuticals, Inc.: C
Topcon Medical Systems, Inc.: L

David Sarraf MD
Amgen, Inc.: C,S
Bayer Healthcare Pharmaceuticals: C,L
Boehringer, Inc.: S
Genentech: C,S
Heidelberg Engineering: S
Iveric Bio: C
Luneau/Optovue: C,L,S
Novartis Pharmaceuticals Corp.: C,L
Regeneron Pharmaceuticals, Inc.: S
Topcon Medical Systems Inc.: S

Shlomit Schaal MD PhD
None

Amy C Schefler MD
Allergan: C
Aura Biosciences: C,S
Castle Biosciences: C,S
Genentech: C,S
Regeneron Pharmaceuticals, Inc.: S

Ursula M Schmidt-Erfurth MD
Apellis Pharmaceuticals, Inc.: C
Genentech: S
Kodiak: S
Novartis Pharma AG: S
RetInSight: P,S
Roche Diagnostics: S

Hendrik P Scholl MD
Astellas Pharma Global Development/ Astellas Institute for Regenerative Medicine: C
Belite Bio: C
Boehringer Ingleheim Pharma GmbH & Co: C
Gerson Lehrman Group: C
Guidepoint Global, LLC: C
Gyroscope Therapeutics Ltd.: C
Janssen Research & Development, LLC: C
Novartis Pharma AG: C
Novo Nordisk: C
Okuvision GmbH: C
ReNeuron Group Plc/Ora, Inc.: C
Tenpoint Therapeutics Ltd.: C

Steven D Schwartz MD
Astellas: S
Horizon Surgical: PS
Nikon: S

Adrienne Williams Scott MD
Alimera Sciences, Inc.: C
Allergan: C
Bausch + Lomb: C
DORC International, bv/Dutch Ophthalmic, USA: C
Genentech: C,S
Novartis Pharma AG: C
Regeneron Pharmaceuticals, Inc.: C

Ingrid U Scott MD MPH
Hoffman La Roche, Ltd.: C
Novartis Pharma AG: C
Regeneron Pharmaceuticals, Inc.: C

Brittni Ashton Scruggs, MD
Illumina Ventures: C

Johanna M Seddon MD
Apellis Pharmaceuticals, Inc.: US
Gemini Therapeutics, Inc.: US
Laboratoires Thea: C

Gaurav K Shah MD
Allergan, Inc.: C,L,S
DORC International: S
Focus Vitamins: SO
OMIC-Ophthalmic Mutual Insurance Company: C
Regeneron Pharmaceuticals, Inc.: C,L,S

Carol L Shields MD
Aura Biosciences, Inc.: C
Immunocore, Inc.: C

Michael A Singer MD
Alimera Sciences, Inc.: S
Allergan: C,L,S
Apellis Pharmaceuticals, Inc.: C,L,S
Aviceda: PS
Bausch + Lomb: C,L
Clearside: C,S
Eyepoint: C,L,S
Genentech: C,L,S
Guidepoint: C
Inflammasome: PS
Iveric: S
Kodiak: C,S
Mallinckrodt Pharmaceuticals: L
Nanoscope: PS
Novartis Pharma AG: C,S
Olives: C,PS
Optos, Inc.: S
Oysterpoint: S
Recent Medical: S
Regeneron Pharmaceuticals, Inc.: L,S
Santen, Inc.: C
Spark Therapeutics, Inc.: C

Rishi P Singh MD
Alcon Laboratories, Inc.: C
Apellis Pharmaceuticals, Inc.: C,S
Asclepix: C
Bausch + Lomb: C
Genentech: C
Gyroscope: C
Novartis: C
Regeneron Pharmaceuticals, Inc.: C
Zeiss: C

Dimitra Skondra MD
Alimera Sciences, Inc.: C
Allergan, Inc.: C
Biogen, Inc.: C
Focuscope: C
Lagrippe Research: C
Neurodiem: C

Lucia Sobrin MD
None

Elliott H Sohn MD
None

Sharon D Solomon MD
None

Richard F Spaide MD
Genentech: C
Heidelberg Engineering: C
Regeneron Pharmaceuticals, Inc.: C
Roche Diagnostics: C
Topcon Medical Systems, Inc.: C,P

Jayanth S Sridhar MD
Alcon Laboratories, Inc.: C
Allergan, Inc.: C
DORC International, bv/Dutch Ophthalmic, USA: C
Genentech: C
Regeneron Pharmaceuticals, Inc.: C

Sunil K Srivastava MD
Adverum: C
Allergan: C,S
Bausch + Lomb: C,S
Carl Zeiss Inc.: C
Clearside: C
Eyevensys: C
Gilead Sciences: C
Novartis Pharma AG: C
Novartis, Alcon Pharmaceuticals: C
Optos, Inc.: C
pSivida: C
Regeneron Pharmaceuticals, Inc.: C
Santen, Inc.: C,S

Giovanni Staurenghi MD
Apellis Pharmaceuticals, Inc.: C
Bayer Healthcare Pharmaceuticals: C
Boheringer: C
Carl Zeiss Meditec: L,S
Centervue: C,L,S
Genentech: C
Heidelberg Engineering: C,L,S
Hoffman La Roche, Ltd.: C,L,S
Iveric: C
Nidek, Inc.: L,S
Novartis Pharmaceuticals Corp.: C,L,S
Ocular Instruments, Inc.: P
Optos, Inc.: S
Optovue, Inc.: S
ORA: C
Quantel Medical: S

Paul Sternberg Jr MD
Novartis Pharma AG: C
Outlook Therapeutics: C

Jennifer K Sun MD
Adaptive Sensory Technology: S
Genentech: S
Novartis: S
Novo Nordisk: S
Optovue: S
Physical Sciences, Inc.: S

Ramin Tadayoni MD PhD
Alcon Laboratories, Inc.: C
Allergan: C
Apellis Pharmaceuticals, Inc.: 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
Thea: C
ThromboGenics, Inc.: C

Tongalp H Tezel MD
None

John T Thompson MD
EHR Command Center, LLC: PS
Genentech: S
Ocutrx Technologies, Inc.: PS

Tanya Trinh MBBS
None

Edmund Tsui MD
Cylite Pty Ltd: S
EyePoint Pharmaceuticals: C
Kowa American Corp.: C,S
Pfizer, Inc.: S

Irena Tsui MD
None

Lejla Vajzovic MD
Aerie Pharmaceuticals, Inc.: L
AGTC: S
Alcon Laboratories, Inc.: C,S
Alderya Therapeutics, Inc.: S
Alimera Sciences, Inc.: C
Allergan, Inc.: C
Apellis Pharmaceuticals, Inc.: C
Bausch + Lomb: C
Beaver-Visitec International, Inc.: C
DORC International, bv/Dutch Ophthalmic, USA: C
Genentech: C
Heidelberg Engineering: S
Iveric Bio: C
Janssen Pharmaceutical: C
Novartis Pharma AG: C
Oculus Surgical, Inc.: C
Orbit Biomedical Inc.: C,S
Regenxbio: C,S
Second Sight Medical Products, Inc.: S

Demetrios Vavvas MD
Olix Pharamceuticals: C
TwentyTwenty: C
Valitor: PS

Nadia Khalida Waheed MD
Bayer Healthcare Pharmaceuticals: S
Boehringer Ingelheim: C
Carl Zeiss Meditec: C,S
Gyroscope Therapeutics: PS,EE
Heidelberg Engineering: C
Johnson & Johnson: C
Nidek, Inc.: C,S
Regeneron Pharmaceuticals, Inc.: C,S
Topcon Medical Systems, Inc.: C

John A Wells III MD
Adverum: C,S
Alimera Sciences, Inc.: S
Bayer Healthcare Pharmaceuticals: S
Genentech: C,S
Gyroscope: S
Iveric: S
Kodiak: 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

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
Genentech: C,L,S
Iveric Bio: C
Merck & Co., Inc.: C
Novartis Pharma AG: C,L,S
Oxurion NV: C
Roche Diagnostics: C,L,S
Samsung Bioepis: C,L
Shanghai Henlius: C
Zhaoke Pharmaceutical: C

Lihteh Wu MD
Bayer Health: C,L
Hoffman La Roche, Ltd.: L
Quantel Medical: C,L

Charles C Wykoff MD PhD
AbbVie: C
Adverum Biotechnologies: C,S
Aerie Pharmaceuticals, Inc.: C,S
AGTC: C
Alderya Therapeutics, Inc.: S
Alexion: S
Alimera Sciences, Inc.: C,S
Alkahest: S
Allergan: C,S
Allgenesis: C
Alnylam Pharmaceuticals: C
Amgen, Inc.: S
Annexon: C,S
Apellis Pharmaceuticals, Inc.: C,S
Arrowhead: C
Asclepix: S
Bausch + Lomb: C
Bayer Healthcare Pharmaceuticals: C,S
Bionic Vision Technologies: C
Boehringer Ingelheim: C,S
Chengdu Kanghong: C,S
Cholgene: C
Clearside Biomedical, Inc.: C,S
Curacle: C
EyePoint: C
Frontera: C
Gemini Therapeutics: S
Genentech: C,S
Graybug Vision: S
Gyroscope: C,S
IACTA: C
Ionis Pharmaceuticals: S
Irenix: S
Iveric Bio (formerly Ophthotech): C,S
Janssen: C
Kato Pharmaceuticals, Inc.: C
Kiora: C
Kodiak Sciences: C,S
Kriya: C
LMRI: S
Nanoscope: S
Neurotech: S
NGM Biopharmaceuticals: C,S
Novartis Pharmaceuticals Corp.: C,S
OccuRx: C
Ocular Therapeutix: C,S
Ocuphire: S
OliX: C
ONL: C,SO
Opthea: C,S
Oxurion: S
Palatin: C
Perfuse Therapeutics: C
PolyPhotonix: C,SO
Ray: C
RecensMedical: C,S,SO
Regeneron Pharmaceuticals, Inc.: C,S
Regenxbio: C,S
Roche: C,S
SamChunDang Pharm: S
Sandoz: S
Stealth: C
Surrozen: C
Taiwan Liposome Co.: S
Thea: C
TissueGen: C,SO
Unity: S
Valo Health: C
Visgenx: SO
Vitranu: C,SO
Xbrane Biopharma: S

Glenn C Yiu MD PhD
AbbVie: C
Adverum: C
Alimera Sciences, Inc.: C
Anlong: C
Bausch + Lomb: C
Carl Zeiss Meditec: L
Clearside Biomedical: S
Endogena: C
Genentech: C
Gyroscope Therapeutics: C
Intergalactic Therapeutics: C
Iridex: L,S
NGM Biopharmaceutical: C
Regeneron Pharmaceuticals, Inc.: C
Thea: C
Topcon Medical Systems, Inc.: C

Yoshihiro Yonekawa MD
Alcon Laboratories, Inc.: C
Alimera Sciences, Inc.: C
Allergan: C
Genentech: C
Pykus: C
Tarsus: C

David N Zacks MD PhD
None

Marco A Zarbin MD PhD FACS
Aerie Pharmaceuticals, Inc.: S
Boerhinger Ingelheim: C
Cell Cure: C
Chengdu Kanghong Biotechnology: C
Daiichi Sankyo: C
Genentech: C
Hoffman La Roche, Ltd.: C
Iduna Therapeutics: C
Illuminare: C
Life Biosciences: C
MantraBio: C
Novartis, Alcon Pharmaceuticals: C,L
NVasc: EO
Ophthotech Corp.: C
Perfuse Therapeutics: C
Rutgers University: P
Seeing Medicines: C
Selphagy: C
Smilebiotech: C

Sandrine Zweifel MD
Alcon Laboratories, Inc.: C
Allergan: C
Apellis Pharmaceuticals, Inc.: C
Bayer Healthcare Pharmaceuticals: C,S
Canon Medical Systems Europe: C
Carl Zeiss Meditec: C
Endogena: C
Novartis Pharma AG: C,S

Presenter Index

Acharya, Nisha 88
Agarwal, Anita 26
Albini, Thomas A 87
Altaweel, Michael M 48
Apte, Rajendra S 77
Arevalo, J Fernando 97
Avery, Robert L 55
Awh, Carl C 51
Bakri, Sophie 145
Baumal, Caroline R 53
Berrocal, Maria H 2
Berrocal, Audina 108
Berry, Jesse L 48
Bhandari, Ramanath 55
Bhisitkul, Robert B 52
Blodi, Barbara Ann 32
Boyer, David S 101
Bressler, Susan B 81
Bressler, Neil M 96
Brown, David 55
Campochiaro, Peter A 114
Chakravarthy, Usha 82
Chan, R V Paul 107
Chang, Stanley 1
Charles, Steven T 6
Cheung, Gemmy Chui Ming 38
Chhablani, Jay K 85
Chiang, Michael F 130
Chow, David R 146
Claes, Carl C 147
Cohen, Michael Nathan 55, 77
Csaky, Karl G 135
Cukras, Catherine A 77
Demirci, Hakan 48
Dhoot, Dilsher S 55
Drenser, Kimberly A 109
Duker, Jay S 76
Duncan, Jacque L 27
Ehlers, Justis P 124
El Rayes, Ehab N 147
Eliott, Dean 141
Fawzi, Amani 26
Ferrone, Philip J 12
Figueroa, Marta 12
Flynn, Harry W 8
Folk, James C 85
Francis, Jasmine 46
Freund, K Bailey 84
Garg, Sunir J 77
Gaudric, Alain 103
Goldstein, Debra A 88
Grigg, John 77
Harbour, J William 45
Hartnett, Mary Elizabeth 105
Hasan, Sohail J 23
Hassan, Tarek S 14
Heier, Jeffrey S 58
Ho, Allen C 110
Holekamp, Nancy M 58
Huang, Suber S 55
Hubbard, G Baker 109
Iezzi, Raymond 12
Ip, Michael S 91
Jabs, Douglas A 86
Jaffe, Glenn J 133
Jhaveri, Chirag D 63
Johnson, Mark W 131
Kaiser, Richard S 54
Kaiser, Peter K 138
Kay, Christine Nichols 77
Kertes, Peter J 55
Khanani, Arshad M 56
Kim, Ivana K 42
Kim, Judy E 54
Kuppermann, Baruch D 99
Lee, Aaron Y 121
Lim, Jennifer Irene 94
Lin, Phoebe 31
Loewenstein, Anat 49, 55
MacCumber, Mathew W 55
Marcus, Dennis M 103
Martin, Daniel F 52
McCannel, Tara A 144
Michaelides, Michel 77
Mieler, William F 26
Miller, Joan W 139
Moshfeghi, Andrew A 85
Moshfeghi, Darius M 109
Mruthyunjaya, Prithvi 48
Muni, Rajeev H 10
Munk, Marion Ronit 76
Murray, Timothy G 143
Nagiel, Aaron 109
Ohno-Matsui, Kyoko 35
Olsen, Timothy W 85
Ozdek, Sengul C 147
Park, Susanna S 117
Patel, Purnima S 103
Pieramici, Dante 53, 55
Pulido, Jose S 26
Querques, Giuseppe 76
Rachitskaya, Aleksandra V 103
Regillo, Carl D 79
Rizzo, Stanislao 147
Rosenfeld, Philip J 25
Sadda, Srinivas R 125
Sarraf, David 78
Schaal, Shlomit 77
Schefler, Amy C 48
Schmidt-Erfurth, Ursula M 128
Scholl, Hendrik P
Schwartz, Steven D 119
Scott, Adrienne Williams 34
Scott, Ingrid U 61
Shah, Gaurav K 12
Shields, Carol L 43
Singer, Michael A 65
Singh, Rishi P 75
Skondra, Dimitra 85
Sobrin, Lucia 88
Sohn, Elliott H 29
Spaide, Richard F 74
Sridhar, Jayanth S 11
Srivastava, Sunil K 88
Staurenghi, Giovanni 83
Sternberg, Paul 13
Sun, Jennifer K 89, 103
Tadayoni, Ramin 67
Tezel, Tongalp H 147
Thompson, John T 18
Trinh, Tanya 22
Tsui, Edmund 88
Tsui, Irena 109
Vajzovic, Lejla 12, 71
Waheed, Nadia Khalida 66, 76
Wells, John A 103
Weng, Christina Y 4
Williams, George A 20
Wong, Tien Yin 122
Wu, Lihteh 26
Wykoff, Charles C 59
Yiu, Glenn C 116
Yonekawa, Yoshihiro 109
Zarbin, Marco A 39
Zweifel, Sandrine 76