A PUBLICATION BY REVIEW of OPHTHALMOLOGY

RETINA SPECIALIST

VOL. 12, NO. 2 · MARCH/APRIL 2026

Double Trouble

Our Robotic OCT & Fundus Camera

Bring the Total Solution to your practice by including Harmony®

Maestro2

Affordable, easy to use spectral domain OCT – now with OCTA[1]

Harmony®

Clinical Image and Data Management Solution

To learn more, visit:
topconhealthcare.com/Maestro2

TOPCON Healthcare

1: US Market

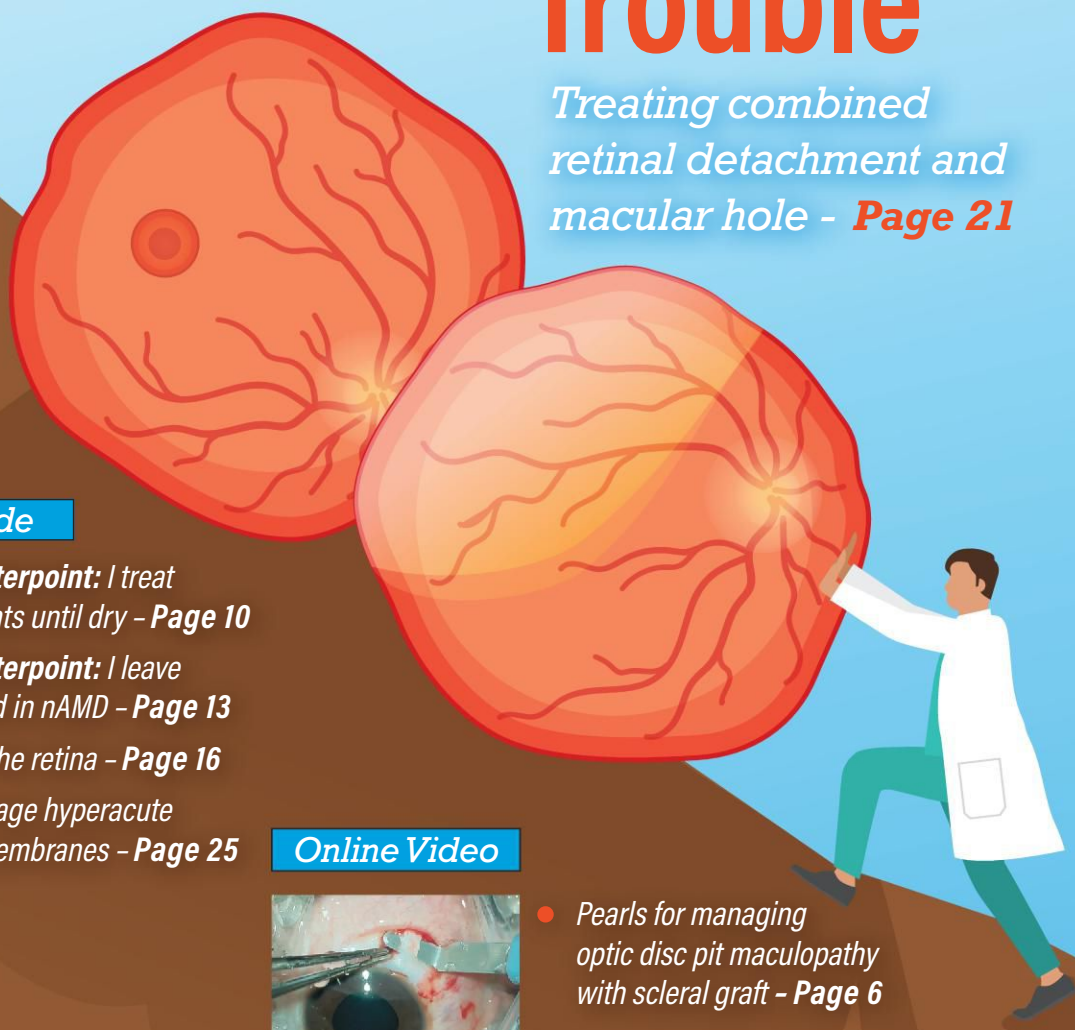
A PUBLICATION BY REVIEW of OPHTHALMOLOGY

RETINA SPECIALIST

VOL. 12, NO. 2 · MARCH/APRIL 2026

Double Trouble

Treating combined retinal detachment and macular hole - ***Page 21***



Also Inside

Online Video

- *Pearls for managing optic disc pit maculopathy with scleral graft –* ***Page 6***

Can One Device Have It All?

SCANMATE FLEX

The Scanmate Flex, a portable ophthalmic ultrasound platform, is the perfect product to enhance your practice's diagnostic capabilities. The Flex provides any desired combination of A-Scan, B-Scan, and UBM.

Its hallmark is flexibility.

DGH TECHNOLOGY, INC.

Serving Eye Care Professionals for over 40 Years

www.dghtechnology.com

(800) 722 3883

sales@dghtechnology.com

RETINA SPECIALIST

19 Campus Blvd., Suite 101
Newtown Square, PA 19073
Telephone (610) 492-1000
Fax (610) 492-1039

Editorial inquiries (610) 492-1000
Advertising inquiries (610) 492-1011
E-mail retinaspecialist@jobson.com

Jobson Medical Information

EDITORIAL

By Jason Hsu, MD

Pondering the Port Delivery System

I consider myself an early adopter, especially when it comes to new technology, ranging from electric cars to surgical heads-up displays. Having been an investigator in the Port Delivery System with ranibizumab (Susvimo, Genentech) trials, I was very excited by the concept of a reservoir that only needs to be refilled every six months or more. Seeing the devastating results of loss to follow-up, this platform seems to be a major mitigation strategy. I remember seeing one wet AMD patient in the Phase II LADDER trial, where device refill-exchanges weren't mandated, who went over a year without needing a refill and was impressed.

So why hasn't this platform taken off? On one hand, it's almost a set it and forget it kind of device at least for six months or longer. One post-hoc analysis of subjects in PAGODA with bilateral DME found that fellow eyes which could be treated with anti-VEGF injections at any time had worse anatomical outcomes than the eyes that received the PDS despite being examined monthly, which makes me wonder if intermittent bolus injections are really a good way to manage disease.

On the flip side, it's a surgical intervention with more risks than an injection, including vitreous hemorrhage, implant dislocation, conjunctival blebs, erosion and retraction. More ominous was the nearly threefold increased risk of endophthalmitis (1.6 percent) in the Phase III ARCHWAY for wet AMD. The Phase III PAGODA and PAVILION (diabetic retinopathy) trials had lower rates—especially endophthalmitis, with no cases of it at one year. Since PAGODA and PAVILION came after ARCHWAY, surgical technique refinements may in part account for the decreasing risks. Alternatively, demographics may be playing a role, given the younger mean age in the diabetic trials where the conjunctiva and Tenon's, which are necessary to cover the implant, are likely thicker.

There's also trepidation about the unknown. When I filled out the recent Preferences and Trends Survey from the American Society of Retina Specialists, only a small minority indicated an interest in the PDS. Our clinics have been steadily fine-tuned to deliver injections, which makes it hard to imagine switching gears. More durable agents are available, with injection intervals potentially reaching four or more months already and new ones, such as the tyrosine kinase inhibitors, expected to exceed that. As a result, I think many of us feel that injecting every six months makes more sense than a permanent device that needs to be refilled at about the same interval.

Ultimately, time will tell where PDS will fall into our armamentarium. Since the device can theoretically deliver various drugs, I can imagine novel therapeutics that may be developed for this platform and help revolutionize retina care. RS

A PUBLICATION BY REVIEW of OPHTHALMOLOGY

RETINA SPECIALIST

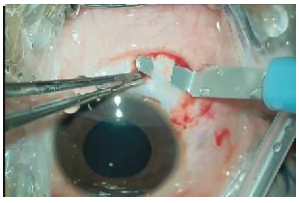
MARCH/APRIL 2026 • VOL. 12, NO. 2

FEATURES

Cover image credit: Getty Images

DEPARTMENTS

Online Video

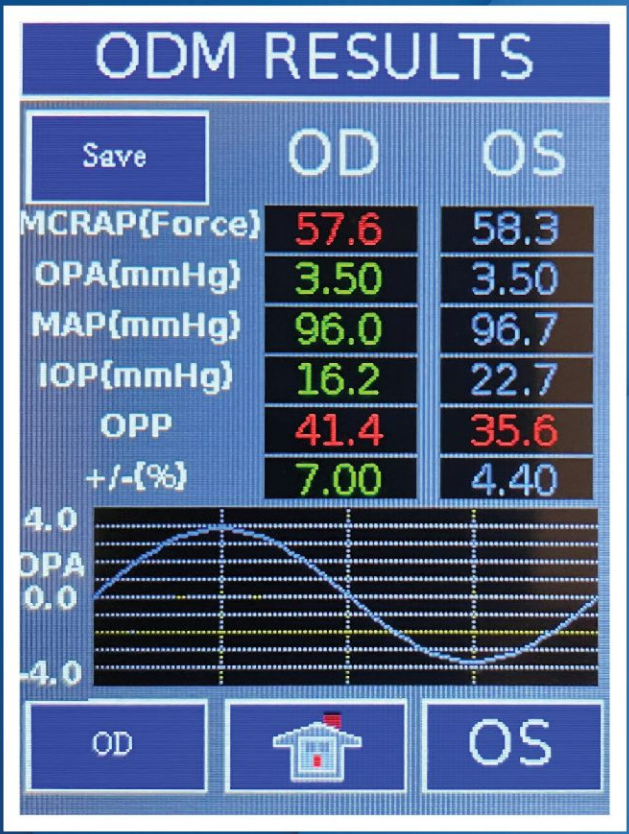


New Advanced FDA Cleared Technology: Measures Ocular Perfusion and Aqueous Outflow*

FALCK MEDICAL™

Falck Multifunction Device

Offers the Best Return On Investment Model of Any Current Eye Care Diagnostic Technology*



"FMD is the only non-invasive, convenient way to measure ocular perfusion, an important metric that's largely underappreciated in understanding retinal diseases."

Shalesh Kaushal, MD, PhD
Founder of Comprehensive Retina Consultants

*Claims made based on accepted clinical trial data, bench testing, and/or internal data.

CAUTION: US Federal Law restricts this device to sale by or on the order of a practitioner.

falckmedical.com

860-536-9000

Optic disc pit maculopathy

Pearls on surgical management of optic disc maculopathy with scleral graft.

Naresh Babu Kannan, MS, FNB, FASRS, Muthu Krishnan V, MS, and Avik Dey Sarkar, MS

Naresh Babu Kannan, MS, FNB, FASRS

Muthu Krishnan, V, MS

Avik Dey Sarkar, MS

BIOS

Dr. Kannan is the head of the Department of Retina & Vitreous Services at Aravind Eye Care System, Madurai, Tamil Nadu, India.

Dr. Krishnan and **Dr. Sarkar** are medical consultants for Retina & Vitreous Services at Aravind Eye Care System, Madurai, Tamil Nadu, India.

Disclosures

The authors have no relevant disclosures.

Optic disc maculopathy can result in serous macular detachment and progressive vision loss. Surgical intervention aims to eliminate subretinal fluid accumulation, restore the macular architecture, and stabilize visual outcomes. Given the rarity of the condition, there currently no universally accepted surgical approach for management.[1] Pars plana vitrectomy with release of vitreoretinal traction and gas tamponade has emerged as the most widely used strategy, with additional maneuvers such as internal limiting membrane peeling, laser photocoagulation, inverted ILM flap or tissue plugging used selectively to block fluid egress through the pit.[1-3] More recently, autologous scleral grafting has been described as a means of creating a mechanical seal at the optic disc pit, with encouraging anatomical and functional outcomes in selected cases.[4,5]

Here, we review a structured approach to managing optic disc maculopathy, with a focus on scleral graft placement and other intraoperative techniques.

Preoperative Assessment

Preoperative optical coherence tomography imaging is critical to evaluate the extent of macular involvement, the level of subretinal fluid, and the pit's exact location. Imaging insights guide the surgical plan and scleral graft dimensions.

Intraoperative Techniques

Following are the steps for achieving a good result:

1. Generous peritomy. Begin with a peritomy to adequately expose the scleral graft harvesting site, ensuring easy access for graft preparation.

2. Scleral graft preparation. Mark the appropriate size and thickness for the graft, then carefully dissect and prepare it for insertion later in the surgery.

3. Pars plana vitrectomy and PVD induction. Perform a pars plana vitrectomy, followed by posterior vitreous detachment induction. This helps reduce vitreoretinal traction around the optic disc.

4. Internal limiting membrane peeling. Conduct a thorough ILM peel around the macula to assist in the redistribution of subretinal fluid and alleviate tangential traction.

5. Fluid-air exchange. Switch to fluid-air exchange to create a stable environment for graft insertion. Ensuring an air-filled vitreous cavity enhances graft positioning and reduces fluid ingress.

6. Port exchange to 23G. Change the dominant port to 23G to facilitate smooth insertion of the prepared scleral graft.

7. Harvesting and insertion of the scleral graft. Retrieve the pre-prepared scleral graft. Insert it through the 20 G port, switching hands may be necessary for precise alignment.

8. Graft positioning. Using gentle movements, guide the graft into the optic disc pit and secure it in place under air. Further drying of the vitreous cavity ensures the graft remains stable.

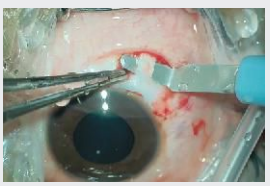
9. Endotamponade with SF6. Inject

(Continued on page 9)

View the Video

A video of the surgeons' structured approach to optic disc maculopathy.

Go to https://bit.ly/4ssJJ7J or scan the QR code.



Department Editor ***Meera Sivalingam, MD***

A Case of Fulminant VKH

A case of bilateral inflammatory disease with excellent recovery in response to prompt treatment.

By Erik Massenzio, MD, and Samantha Massenzio, MD

Erik Massenzio, MD

Samantha Massenzio, MD

A 45-year-old Black female with no past medical or ocular history presented with blurry vision in both eyes after one week of severe headache. Snellen visual acuity was counting fingers in both eyes. Intraocular pressures were normal in both eyes. Anterior segment examination was normal and there were 1+ cells in the anterior vitreous of both eyes.

Fundoscopic examination of both eyes demonstrated normal optic discs and normal vasculature; however, there were 360 degrees of serous choroidal detachments and large pockets of subretinal fluid throughout the macula and mid-periphery *(Figures 1, 2)*. Fundus autofluorescence demonstrated hyperautofluorescence within the pockets of subretinal fluid in the macula and mid-periphery of both eyes *(Figure 3)*. Fluorescein angiography revealed diffuse leakage of the peripheral vessels in both eyes and pooling corresponding to the pockets of subretinal fluid in both eyes. There were pinpoint areas of hyperfluorescence, most notable in the left eye, reminiscent of a "starry sky" appearance *(Figure 4)*. Indocyanine green angiography revealed mixed hyper- and hypofluorescence of the macula. Optical coherence tomography of both eyes demonstrated multiple areas of large bacillary detachments in both eyes *(Figures 5, 6)*.

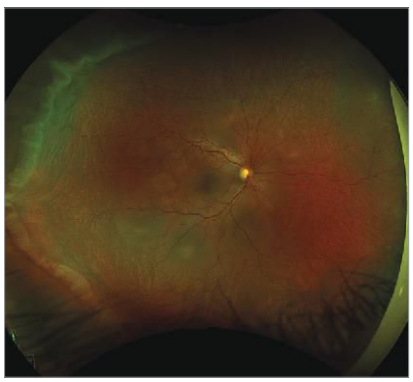


Figure 1. Pseudo color fundus photo of the right eye with 360 degrees of serous choroidal detachments, bacillary detachments, and exudative subretinal fluid.

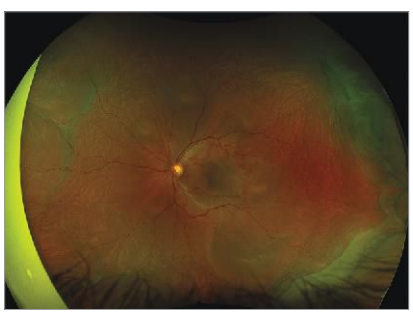


Figure 2. Pseudo color fundus photo of the left eye with 360 degrees of serous choroidal detachments, bacillary detachments and exudative subretinal fluid.

Our differential diagnosis for this patient included Vogt-Koyanagi-Harada disease, bilateral posterior scleritis, sarcoidosis, lymphoma, uveal effusion syndrome, malignant hypertension, syphilis and tuberculosis. A broad laboratory workup for these infectious and inflammatory etiologies was ultimately negative. The diagnosis of VKH disease was made based on the patient's clinical presentation and imaging findings.

The patient was started on topical difluprednate four times daily in both eyes, atropine twice daily in both eyes and oral prednisone dosed at 1 mg/kg per day. After two weeks, the bacillary detachments were noted to have worsened, and the patient's vision subjectively declined further to hand motions in both eyes. At this time, the decision was made to admit the patient for pulse-dose steroids with initiation of infliximab. The patient completed five days of IV methylprednisolone 250 mg administered every six hours. Rheumatology was consulted to initiate infliximab.

One week after pulse-dose steroids and starting infliximab, the bacillary detachments had completely resolved in both eyes, with improvement of visual acuity to 20/80 in the

BIOS

Erik Massenzio, MD, is a retina fellow at Wills Eye Hospital.

Samantha Massenzio, MD, is a third-year resident at Wills Eye Hospital.

right eye and 20/70 in the left eye.

The patient was continued on infliximab dosed at 5 mg/kg every eight weeks, and oral prednisone was decreased by 5 mg per week.

After one month of being off prednisone, her serous choroidal detachments and bacillary detachments recurred. The patient was restarted on 40 mg daily of prednisone, and her infliximab was increased to 7.5 mg/kg. After tapering the prednisone following this flare, she was continued on infliximab at 7.5 mg/kg for an additional one and a half years.

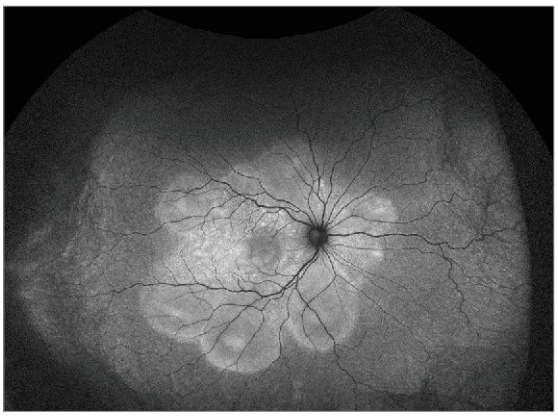


Figure 3. Fundus autofluorescence of the right eye demonstrating hyper autofluorescence corresponding to pockets of subretinal fluid and bacillary detachments, degrees of serous choroidal detachments, bacillary detachments and exudative subretinal fluid.

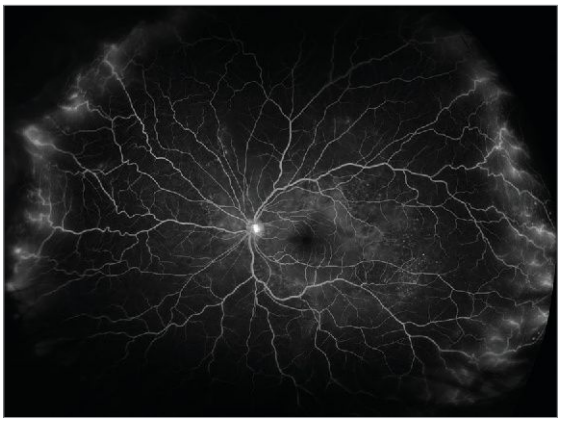


Figure 4. Fluorescein angiogram of the left eye revealing diffuse leakage of peripheral vessels and "starry sky" appearance of the temporal midperiphery.

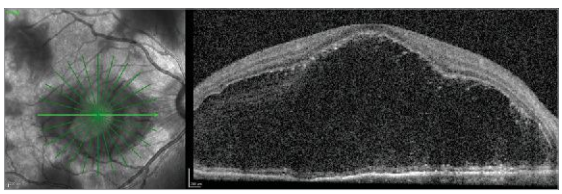


Figure 5. OCT of the right eye demonstrating a massive bacillary detachment.

The patient has now remained stable for one year after stopping infliximab, and her visual acuity has improved to 20/20 in both eyes.

Discussion

VKH disease is a rare autoimmune disorder characterized by anterior and posterior uveitis, vitiligo, headache and hearing loss.1 Classically, VKH is divided into four stages: First, the prodromal stage, which typically includes fevers, headaches and neck pain. Second, the uveitic stage, featuring anterior or posterior uveitis including classic features such as choroidal detachments with subretinal fluid and bacillary detachments with a starry sky appearance on fluorescein angiogram, many of which were seen in our case. Third, the chronic stage describes the development of vitiligo, depigmentation of the choroid and poliosis. Fourth, the recurrent stage describes acute recurrences of uveitis, most commonly anterior uveitis.

Treatment of VKH involves steroids and immunomodulatory therapy. Numerous studies recently have advocated for early treatment with immunomodulatory therapy in order to improve the relentless course of this inflammatory disease.[1-3] In one study, when immunomodulatory therapy was initiated within six weeks of presentation, patients had a better visual outcome at four years that was statistically significant.[4] As for choice of immunomodulatory therapy, anti-TNF agents have become popular; however, other agents including azathioprine, cyclosporine and mycophenolate have also been used.[5]

In this case, the presence of a bacillary detachment was critical for making the diagnosis of VKH in a timely manner. "Bacillary" means "shaped like a rod"; a bacillary layer detachment is named as such because photoreceptors are approximately rod-shaped, and the detachment involves splitting of the photoreceptors at the level of the inner segment myoid. It can be recognized on OCT as fluid between the ellipsoid zone and the external limiting membrane.

In terms of mechanism, one hypothesis is that a bacillary layer detachment occurs when the accumulation of subretinal fibrin modulates the adhesion between the photoreceptor outer segments and the apical microvilli of the retinal pigment epithelium.[6] Subretinal exudation then exerts hydrostatic pressure, leading to the bacillary layer detachment.

In a literature review of cases of bacillary detachments, most reported cases of bac-

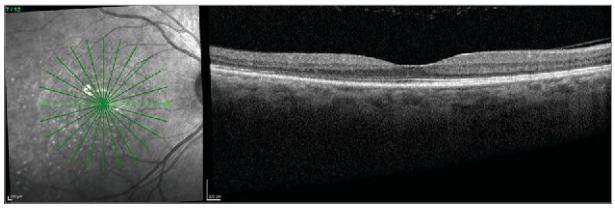


Figure 6. OCT of the left eye revealing mixed subretinal fluid and bacillary detachments.

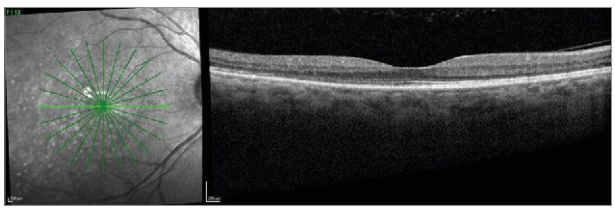


Figure 7. OCT of the right eye one year after stopping infliximab.

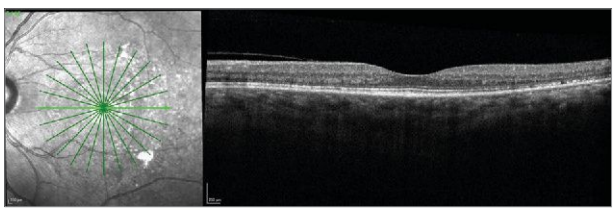


Figure 8. OCT of the left eye one year after stopping infliximab.

illary layer detachments were seen in VKH and other inflammatory diseases.[6]

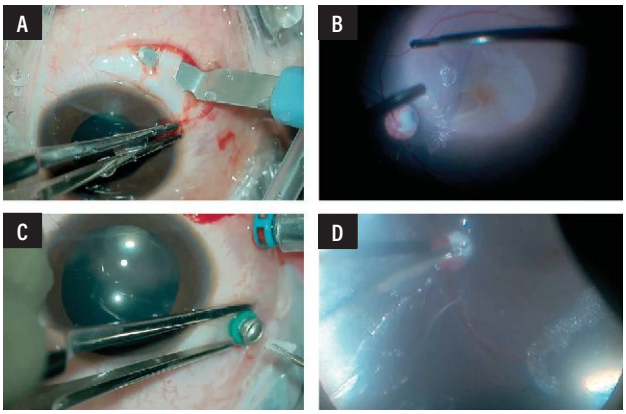
The Bottom line

When VKH syndrome is suspected, prompt treatment with steroids and immunomodulatory agents is important. Presence of bacillary layer detachment can lead to higher suspicion of VKH syndrome, especially in the right clinical context, although it can also be found in other inflammatory diseases. With prompt and effective treatment, patients can achieve remarkable restoration of their vision.

REFERENCES

1. Lavezzo MM, Sakata VM, Rodriguez EEC, et al. Subclinical signs persistence in Vogt-Koyanagi-Harada disease (VKHD) patients treated with early high-dose corticosteroids and immunosuppressive therapy (IMT). Investigative Ophthalmology & Visual Science 2018;59:9:422-422.
2. Urzua CA, Velasquez V, Sabat P, et al. Earlier immunomodulatory treatment is associated with better visual outcomes in a subset of patients with Vogt-Koyanagi-Harada disease. Acta ophthalmologica 2015;93:6:e475-e480.
3. Paredes I, Ahmed M, Foster CS. Immunomodulatory therapy for Vogt-Koyanagi-Harada patients as first-line therapy. Ocular immunology and inflammation 2006;14:87-90.
4. Oo EEL, Chee SP, Wong KKY, et al. Vogt-Koyanagi-Harada disease managed with immunomodulatory therapy within 3 months of disease onset. American Journal of Ophthalmology 2020;220:37-44.
5. Rahman N, Artiaga JC, Bouras K, et al. Immunosuppressive therapy for Vogt-Koyanagi-Harada disease: A retrospective study and review of literature. Journal of Ophthalmic Inflammation and Infection 2023;13:1:27.
6. Ramtohul P, et al. Bacillary layer detachment: Multimodal imaging and histologic evidence of a novel optical coherence tomography terminology: Literature review and proposed theory. Retina 2021;41:11:2193-2207.

(Continued from page 6)



Adequate size and thickness of the scleral graft is dissected and prepared (A). Following ample ILM peeling (B), the scleral graft inserted through a 23G vitrectomy port (C) and gently inserted into the optic disc pit (D).

SF6 gas to provide endotamponade, helping to maintain graft positioning and prevent fluid re-accumulation. Instruct patients on face-down positioning postoperatively to optimize graft contact.

Postoperative Management

Postoperatively, patients should maintain a face-down position to support graft adhesion and reduce subretinal fluid recurrence. Regular follow-ups with OCT imaging are recommended to monitor macular reattachment and ensure graft stability.

The Bottom Line

The combined technique of vitrectomy, ILM peeling, autologous scleral graft plugging and gas tamponade represents a logical and robust strategy for optic disc maculopathy. By addressing both tractional and communication-based mechanisms of fluid accumulation, it may improve the likelihood of durable macular reattachment in complex cases.

REFERENCES

1. Moisseiev E, Moisseiev J, Loewenstein A. Optic disc pit maculopathy: When and how to treat? A review of the pathogenesis and treatment options. Int J Retina Vitreous 2015;1:13.
2. Iros M, Parolini B, Ozdek S, Gini G, Nawrocka ZA, Ellabban AA, Faramawi MF, Adelman R, Sallam AB; EVRS Study Group. Management of optic disc pit maculopathy: The European VitreoRetinal Society optic pit study. Acta Ophthalmol 2022;100:6:e1264-e1271.
3. Zheng A, Singh RP, Lavine JA. Surgical options and outcomes in the treatment of optic pit maculopathy: A meta-analysis and systematic review. Ophthalmol Retina 2020;4:3:289-299.
4. Babu N, Kohli P, Ramasamy K. Comparison of various surgical techniques for optic disc pit maculopathy: vitrectomy with internal limiting membrane (ILM) peeling alone versus inverted ILM flap 'plug' versus autologous scleral 'plug'. Br J Ophthalmol 2020;104:11:1567-1573.
5. Shah PK, Karandikar SS, Narendran V. Scleral autograft for optic nerve head pit associated chronic maculopathy. Ophthalmic Surg Lasers Imaging Retina 2017;48:3:251-254.

Point-Counterpoint

Why I treat wet AMD patients until dry

Treating patients until dry optimizes long-term vision.

By Nikolas J.S. London, MD, FACS, and Thomas Lazzarini, MD

Nikolas J.S. London, MD, FACS

Thomas Lazzarini, MD

Take-home points

- All intraretinal fluid and most subretinal fluid should be eliminated to maximize visual outcomes in neovascular AMD.
- Fluid-tolerant strategies risk normalizing undertreatment in real-world settings where OCT interpretation and follow-up adherence vary.
- Treating to anatomic dryness provides a clear, objective endpoint and enables safe interval extension while minimizing long-term complications.

Anti-VEGF therapy transformed neovascular AMD from a blinding disease to one we can manage. But we still argue about the endpoint: complete anatomic dryness on OCT, or tolerance of some residual fluid, particularly small-volume subretinal fluid. My practice reflects the evidence through 2025, which consistently favors treating until dry: completely eliminating intraretinal fluid and minimizing subretinal fluid to optimize long-term vision.

Not all fluid behaves the same

Post-hoc analyses of CATT, HARBOR, and VIEW taught us that intraretinal fluid, especially when it involves the fovea, predicts worse visual outcomes.[1,10] In HARBOR, residual IRF meant diminished vision gains regardless of location or severity.[1] Subretinal fluid showed a more variable relationship with acuity, and residual SRF at 24 months didn't correlate with worse vision in that analysis.

But we shouldn't oversimplify this into blanket SRF tolerance. A 2025 systematic review found persistent fluid in 41 percent of eyes at one year and 47 percent at two years despite ongoing treatment.[3] The key finding: Mean visual acuity was significantly better in eyes without any fluid. Limited SRF may be tolerable in select cases under rigorous follow-up and monitoring protocols, but across broad patient populations in the real world, a completely dry retina consistently delivers superior functional outcomes.

What FLUID actually tells us

The FLUID study gets cited frequently to justify fluid tolerance. It demonstrated non-inferior vision when allowing up to 200 µm of SRF in a treat-and-extend protocol.[2] Look closer at what FLUID required: continuous anti-VEGF therapy regardless of fluid status—treatment never stopped. IRF resolution was mandatory before extending intervals. And the injection burden difference was modest, only 1.2 fewer injections over two years (15.8 versus 17).

FLUID supports selective SRF tolerance only within rigorous, ongoing therapy with mandatory IRF clearance. It's not a license for undertreatment or accepting any IRF.

BIOS

Dr. London is president of the San Diego Retina Research Foundation, the founder and president of the Ophthalmology Society of San Diego and chief of Ophthalmology at Scripps Memorial Hospital in La Jolla, Calif.

Dr. Lazzarini is an associate vitreoretinal surgeon at Retinal Consultants of San Diego.

The real-world problem: We undertreat

Clinical trials run on idealized schedules with protocol-driven imaging and strict retreatment criteria. Real-world registries tell a different story: fewer injections, longer intervals, and delayed detection of recurrence.[5,6] These patterns consistently produce worse visual outcomes than trial results.

When you adopt a fluid-tolerant strategy in real-world practice, you risk normalizing undertreatment. The TRUCKEE study illustrates this perfectly.[7] Among patients switched to faricimab because of suboptimal response to prior therapy, more than 80 percent still had residual IRF and more than 60 percent had residual SRF after the first injection. These numbers highlight both how common persistent fluid is in routine practice and how difficult achieving dryness can be when patients have been undertreated.

Fluid fluctuations cause particular harm. Recent HAWK and HARRIER analyses as well as real-world data confirm that greater fluid stability—more visits with dry retinas—correlates with larger vision gains.[9, 10] In fact, patients whose retinas were consistently dry after loading had better visual and anatomic outcomes.[11] SRF that fluctuates or increases between visits often heralds IRF recurrence and progressive photoreceptor injury. That small amount of SRF you note at one visit can become significant by the next if you've stretched the interval or if imaging review isn't meticulous.

OCT interpretation isn't as reliable as we think

Here's something we don't discuss enough: OCT interpretation is operator-dependent. CATT data showed treating ophthalmologists miss or misclassify fluid compared with reading centers.[8] This matters enormously when you adopt permissive strategies, you're more likely to miss opportunities for timely retreatment.

Treating to anatomic dryness gives you a clear, objective endpoint, as well as a clear indication of increased or recurrent disease activity. It eliminates the interpretive ambiguity about what constitutes "acceptable" residual fluid and reduces the risk of silent progression between visits.

Long-term structural damage from persistent fluid

Chronic fluid exacts a structural toll beyond immediate acuity measures. Real-world data link persistent fluid to outer retinal atrophy, complete RPE and outer retinal atrophy, and increased subretinal fibrosis, all strongly tied to visual decline. About half of nAMD patients develop subretinal fibrosis by two years despite anti-VEGF therapy. Fibrosis and atrophy together drive irreversible vision loss.

The ellipsoid zone serves as our key biomarker for photoreceptor health. Chronic IRF correlates with progressive EZ disruption and consequent vision loss. Each fluid recurrence likely inflicts incremental photoreceptor damage that accumulates over years. Early and sustained fluid resolution preserves the retinal microarchitecture photoreceptors needed for long-term function.

How I implement this approach

I use treat-and-extend with a low threshold for treating new or persistent fluid. After three monthly loading doses, I extend intervals only when IRF is fully resolved and SRF is minimal or absent. High-quality OCT matters. I review the entire macular volume, not just central subfield thickness, looking carefully for subtle parafoveal IRF and assessing EZ integrity. This approach allows me to strike a balance between the known risks of undertreatment, while also avoiding potential risks associated with ongoing monthly therapy.

Patient education on adherence is critical. The "treat until dry" philosophy only works with sustained engagement over years of care.

Balancing aggressive treatment with individualization

My goal is anatomic quiescence—a dry retina—that permits safe interval extension.

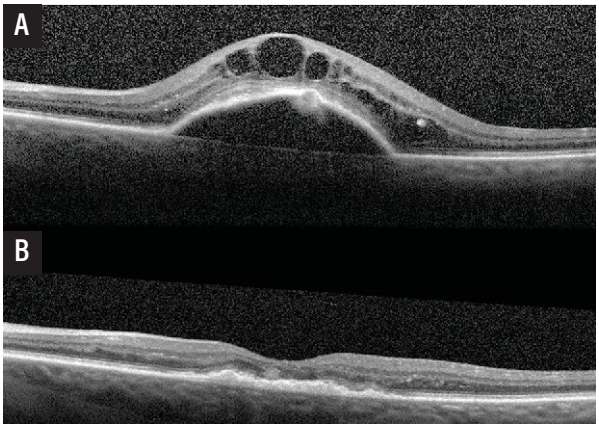


Figure 1. Optical coherence tomography images demonstrating treatment response to intravitreal anti-VEGF therapy in treatment naive neovascular age-related macular degeneration. (A) Baseline OCT of the left eye at the time of presentation with neovascular AMD demonstrating a fibrovascular pigment epithelial detachment, subretinal hyperreflective material (SRHM), and intraretinal fluid. (B) Follow-up OCT of the same eye following three monthly loading intravitreal anti-VEGF injections demonstrating marked reduction in PED height and complete resolution of IRF—illustrating the robust anatomic response that supports a treat-until-dry management approach.

Many patients reach 12-week intervals while maintaining complete fluid resolution; others need more frequent treatment. I guide management by anatomic endpoints, not arbitrary calendar-based intervals, which allows for appropriately tailored therapy in a population of patients with heterogeneous medication-response and underlying disease activity.

Clinical judgment remains essential. For frail or elderly patients where treatment risks outweigh benefits or goals differ, I modify the approach after careful discussion. But for most nAMD patients, aggressive fluid elimination offers the best chance at preserving vision long-term. With patients living longer and healthier than ever before, this is what matters to them. Emerging agents and delivery systems (higher-dose aflibercept, brolucizumab, Susvimo, gene therapies like sura-vec/ABBV-RGX-314) aim to maintain dryness with fewer interventions, which strengthens this philosophy.

The atrophy question

The concern about intensive anti-VEGF dosing accelerating geographic atrophy is legitimate. CATT showed higher GA risk with monthly versus PRN dosing,[4] and VEGF is a trophic factor for RPE, photoreceptors and choriocapillaris.

But untreated or inadequately treated CNV, variation in retinal thickness and chronic fluid also drive atrophy through inflammation, RPE dysfunction and photoreceptor loss. The question becomes: What causes more harm, recurrent inadequately controlled exudation or VEGF suppression itself? Current evidence supports achieving early stability (a dry retina), then carefully extending intervals to minimize both cumulative anti-VEGF exposure and tissue damage from recurrent fluid.

Conclusion

Fluid-tolerance data have refined our approach, but the bulk of evidence through 2025 supports treating nAMD until the retina is dry. This strategy optimizes visual acuity, preserves critical microarchitecture and reduces long-term complications like fibrosis and atrophy. In the real world, where follow-up and imaging quality vary, an explicit treat-to-dry strategy reduces undertreatment risk and provides a clear therapeutic target.

"Treat until dry" isn't overtreatment—it's adequate treatment. That distinction makes all the difference in preserving our patients' vision over years of disease.

REFERENCES

1. Holekamp NM, et al. Relationship between retinal fluid characteristics and vision in neovascular age-related macular degeneration: HARBOR post hoc analysis. Br J Ophthalmol 2022;106:11:1595-1603.
2. Guymer RH, et al. Tolerating subretinal fluid in neovascular age-related macular degeneration treated with ranibizumab using a treat-and-extend regimen: FLUID study 24-month results. Ophthalmology 2019;126:5:723-734.
3. Patil NS, et al. Persistence of retinal fluid after anti-VEGF treatment for neovascular age-related macular degeneration: A systematic review and meta-analysis. Ophthalmol Retina 2025;S2468-6530:25:00012-0.
4. Grunwald JE, et al. Risk of geographic atrophy in the comparison of age-related macular degeneration treatments trials. Ophthalmology 2014;121:1:150-161.
5. Wykoff CC, et al. Impact of anti-VEGF treatment and patient characteristics on vision outcomes in neovascular AMD: Up to 6-year analysis of the AAO IRIS Registry. Ophthalmol Sci 2023;4:2:100421.
6. Holz FG, et al. Key drivers of visual acuity gains in neovascular AMD in real life: Findings from the AURA study. Br J Ophthalmol 2016;100:12:1623-8.
7. Khanani AM, et al. The real-world efficacy and safety of faricimab in neovascular age-related macular degeneration: The TRUCKEE study – 6 month results. Eye 2023;37:3574-81.
8. Toth CA, et al. Identification of fluid on optical coherence tomography by treating ophthalmologists versus a reading center in the CATT. Retina 2015;35:7:1303-14.
9. Chakravarthy U, et al. Impact of macular fluid volume fluctuations on visual acuity during anti-VEGF therapy in eyes with nAMD. Eye (Lond) 2021;35:11:2983-90.
10. Dugel PU, et al. Effect of retinal thickness variability on visual outcomes and fluid persistence in neovascular age-related macular degeneration: a post hoc analysis of HAWK and HARRIER studies. Retina 2022;42:3:511-518.
11. Eichenbaum, et al. Impact of retinal fluid-free months on outcomes in neovascular age-related macular degeneration: a treatment agnostic analysis of the HAWK and HARRIER studies. Retina 2023;43:4:632-640.

Point-Counterpoint

Why I tolerate some fluid after treating wet AMD patients

Tolerating a stable amount of fluid may allow us to extend treatment intervals, and may be beneficial to vision in the long run.

By Robyn Guymer, MBBS, PhD, FRANZCO

Take-home points

- In nAMD, traditional treat-and-extend regimen dictates that extensions can't occur if there's any residual fluid, hence the clinician is stuck with short treatment intervals even when all parameters are stable.
- In nAMD eyes with stable subretinal fluid that persists despite frequent injections, careful extension will often allow greater intervals with less treatment burden and no untoward consequences.
- In nAMD, mature sub RPE vessels may leak a little, but may also be protecting against atrophy and can be tolerated and, in some cases, have led to better vision outcomes than a dry retina.

Robyn Guymer, MBBS, PhD, FRANZCO

As we moved from a "one size fits all" anti-vascular endothelial growth factor treatment for exudative macular neovascularization, secondary to age-related macular degeneration, to individualized treatment intervals, it was necessary for clinicians to make an assessment of the VEGF-driven disease activity. In the now widely adopted treat-and-extend regimens for anti-VEGF treatment in neovascular AMD, determining VEGF-driven disease activity is required, as it dictates the next treatment interval: increasing the interval if the disease is deemed inactive, or decreasing it if the disease is active. Identifying ongoing disease activity in the setting of ongoing treatment for nAMD largely comes down to the presence or absence of fluid in the retina. Thus, the presence of black spaces on an OCT scan has become the surrogate biomarker for VEGF-driven disease activity. Unfortunately, this biomarker isn't perfect, its presence doesn't always imply VEGF-driven exudative neovascular disease activity, and as such requires a nuanced interpretation, both at diagnosis and in the ongoing management of nAMD.[1]

At diagnosis, clinicians need to be sure the black spaces in the retina, which may at times be discovered incidentally on routine imaging, without any symptoms, are truly due to exudative nAMD, and not another cause commonly misinterpreted as exudative AMD such as pseudovitelliform lesions, central serous chorioretinopathy, macular telangiectasis (MacTel), draping between two drusenoid PEDs, or fluid not uncommonly seen at the apex of large pigment epithelial detachments (PEDs) or degenerative cysts associated with the early signs of atrophy.[2-5]

Assuming the correct diagnosis, then treatment-naïve exudative MNV should be treated without delay, with the initial "loading" phase of treatment aiming to stop the exudation as rapidly as possible. The aim is to return the retinal anatomy to as near normal as possible, as soon as possible.

The question is: What to do if, despite this intense initial phase of treatment (or at some later time point in treatment) and de-

BIOS

Dr. Guymer is deputy director of the Centre for Eye Research Australia, the head of macular research at CERA, and professor of ophthalmology at the University of Melbourne. She's also a senior retinal specialist at The Royal Victorian Eye and Ear Hospital.

spite ongoing regular treatment every four to six weeks, not all fluid is resolved? In a strict treat-and-extend protocol, which allows for no fluid before interval extension, the intervals shouldn't be increased. This would then mean that a patient might be treated monthly with an anti-VEGF indefinitely if the fluid fails to completely resolve, and the eye will be labeled a "hungry" eye or a "failure to respond" eye. Likely the patient will be changed to different drugs in the hope of extending the interval between injections, often with no success. This patient might even be enrolled into a new drug trial for people who are deemed to "require" frequent injections.

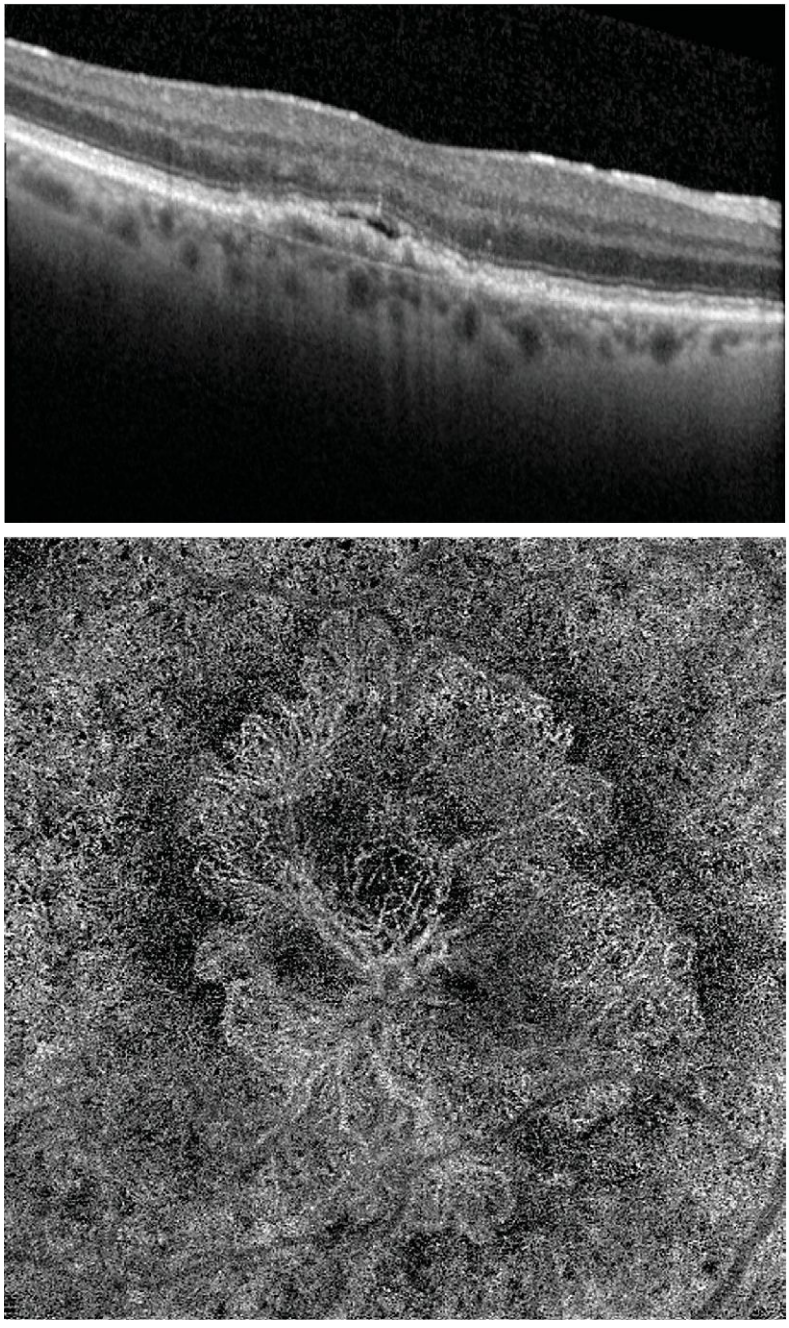


Figure 1. OCT B Scan of a patient who'd been treated with anti-VEGF treatment two years ago. A small amount of SRF persists while visual acuity remains stable and OCT angiography shows the large mature vessel complex.

Is there another way to handle this scenario? Clearly if the fluid is increasing, or new, one has to assume that it's due to VEGF-driven diseases (even if there is some doubt), but because it's new/increasing, the safest option (first do no harm) is to assume it's due to VEGF and decrease the interval to see if you can improve the situation.

The question is really around stable fluid—give or take a few microns. Could some apparently stable fluid be tolerated, allowing the interval to increase and the treatment burden to be reduced?

Dealing with intraretinal fluid first. Exudative cysts are defined by their quick resolution after anti-VEGF therapy, whereas degenerative cysts persist.[6] Many studies have shown that IRF, secondary to exudative nAMD, is associated with poorer visual acuity outcomes and an increased risk of developing atrophy and fibrosis, both of which contribute to vision loss.[7-10] In the CATT trial, with respect to fluid, IRF was found to have the greatest impact on vision at all time points.[11]

Thus, IRF should be treated, with the aim to resolve these cysts, but if they persist, then consider if they could be atrophic. This might especially be the case if they appear above areas suggestive of early atrophy such as signal hypertransmission into the choroid, or retinal pigment epithelial loss.[12]

Also consider: Could the cystic spaces not be a result of nAMD? This is where fluorescein angiography would help en-

sure the diagnosis is correct, proving that these spaces aren't due to diseases such as MacTel. In the setting of nAMD, if IRF isn't going away or decreasing, despite intensive treatment with short intervals, consider cautious extension, even by one week at a time. If the IRF increases, then you have the answer—they're likely a result of VEGF-driven disease, so they appear to need ongoing short-interval treatment. If they stay the same, then try another week's extension.

With regard to tolerating fluid in the setting of true exudative nAMD, the main question to consider relates to subretinal fluid. One scenario to explain stable SRF not responding to anti-VEGF, in the setting of actual nAMD, is that these black spaces aren't related to ongoing exudation and unchecked VEGF activity, but rather may be a result of draping, failure of the outer retina to reattach to the RPE, possibly due to osmotic pressure in the space due to residual material. In which case, one could consider slowly extending the interval, perhaps by only a week at a time. If, in so doing, the fluid increases, then one has to assume it's active, exudative, VEGF-driven disease, but if it stays relatively the same then continuing cautious extension should be considered.

Another scenario is that possibly the persistence of SRF in the setting of nAMD is truly indicative of a small amount of exudation. But maybe this isn't all bad. The presence of SRF at baseline and persistence of SRF have been associated with better long-term visual acuity.[7-9]

Thus, there's evidence to suggest that allowing some residual SRF isn't detrimental and may actually be beneficial to vision. In an analysis of data from patients with nAMD in the IVAN trial, the presence of SRF at the final visit halved the probability of atrophy developing within the nAMD lesion (odds ratio [OR] 0.41; p=0.004),[13] with similar findings reported in other studies.[14,15]

One study in nAMD found that the presence of SRF at 36 months was associated with a lower rate of fibrosis (OR 0.49; 95% confidence interval [CI] 0.29–0.81) and fibrosis progression (OR 0.50; 95% CI 0.31–0.81) (both p=0.005).[15] In these studies, poor visual outcomes are often associated with the development of atrophy and fibrosis rather than with incomplete treatment of VEGF-driven MNV activity.[16]

It's possible that the maturing MNV under the RPE "oozes" a little from time to time but does no harm, and indeed is providing oxygen and nutrients to reduce the risk of atrophy.

Even under prolonged VEGF suppression, persistence of flow within mature vessels has been demonstrated in eyes with type 1 neovascular lesions *(Figure 1)*.[16]

In these cases of stable SRF, tolerating a small amount of SRF and small fluctuations in the SRF may be okay, with the possibility that the ultimate aim of treatment is to achieve a stage of mature non-exudative vessels that continue to nourish the outer retina, but from time to time may leak a little.

The FLUID study was a pioneering work, advocating a tolerant approach towards small amounts of residual SRF.[17] Recent American Society of Retina Specialists surveys tried to gauge physicians' tolerance for fluid in nAMD, and found that consistently around half of participating physicians indicated that they would maintain treatment intervals and tolerate some SRF.[18]

Yet clinical practice guidelines from the American Academy of Ophthalmology, the Royal College of Ophthalmologists in the United Kingdom and the European Society of Retina Specialists all state that fluid on OCT is an indication of active disease and recommend retreatment when fluid is present.[19-21]

However, the Vision Academy recently published a consensus guidelines paper where they state that "small amounts of persistent fluid could be tolerated without

(Continued on p. 20)

There's evidence to suggest that allowing some residual subretinal fluid isn't detrimental and may actually be beneficial to vision.

GLP-1 receptor agonists and the retina

What to watch for and how to manage any issues that occur.


Ashley Zhou, MD


Andrew J. Barkmeier, MD

By Ashley Zhou, MD, and Andrew J. Barkmeier, MD

Take-home points

- The current evidence doesn't support avoiding or delaying GLP-1 RA out of concern for diabetic retinopathy complications.
- Closer follow-up may be warranted for patients with anticipated or observed rapid HbA1c reduction after GLP-1 RA initiation.
- Ongoing basic and translational research will continue to elucidate class-specific and drug-specific effects on diabetic retinal disease.

Glucagon-like peptide 1 receptor agonists are paradigm-shifting medications, helping many patients manage their diabetes, aiding with weight loss and reducing risk of serious health complications. Even with their significant potential benefits, however, GLP-1 RAs come with safety warnings for patients to speak with their doctor before starting treatment if they have a history of diabetic retinopathy. Patients and colleagues in other specialties are going to seek the input of retina specialists regarding the use of GLP-1 RAs. Therefore, it's imperative to understand what the data tells us about GLP-1 RAs and diabetic retinopathy. Here we'll outline what you need to know to aid patients and your colleagues when they come to you for answers.

The rise of GLP-1 RAs

As a retinal specialist, many of your patients are already using GLP-1 RAs and many more will receive new prescriptions in the near future. Survey data from the National Center for Health Statistics published in 2025 show that more than a quarter (26.5 percent) of adults diagnosed with diabetes are using GLP-1 RAs.[1] In addition to the growth in usage among patients with diabetes, GLP-1 RA prescriptions are rising rapidly in the broader U.S. population, with the share of GLP-1 RA fills for non-diabetes-related conditions nearly doubling from 7.4 percent in 2019 to 14.3 percent in 2022.[2]

There are six FDA-approved GLP-1 RAs on the market, including several that are widely recognized in the popular media: exenatide (Byetta, Bydureon); liraglutide (Victoza, Saxenda); dulaglutide (Trulicity); lixisenatide (Adlyxin); semaglutide (Ozempic, Rybelsus, Wegovy); and tirzepatide (Mounjaro, Zepbound, which works as a dual GLP-1/GIP [glucose-dependent insulinotropic polypeptide] agonist). Recently, an oral formulation of Wegovy and a new oral GLP-1, Foundayo (Lilly), were approved, which could increase adoption rates of these drugs even further.

These agents mimic GLP-1, an endogenous incretin hormone released in response

BIOS

Dr. Zhou is a PGY-3 ophthalmology resident at the Mayo Clinic in Rochester, Minnesota.

Dr. Barkmeier is a professor of ophthalmology at the Mayo Clinic in Rochester.

to eating. In doing so, GLP-1 RAs stimulate insulin release while suppressing glucagon secretion and slowing gastric emptying, ultimately reducing appetite.[3] But the effects of GLP-1 RAs are even more sweeping. GLP-1 receptors are present in many tissues ranging from the brain to the heart to the retinal pigment epithelium.[4,5] In the retina, pre-clinical studies have revealed potentially anti-inflammatory and neuroprotective effects independent of glucose-lowering effects.[6]

Importantly, these are life-saving therapies, independent of any impact they may have on the eye. A recent meta-analysis of 11 randomized controlled trials demonstrated a 13-percent relative risk reduction for all-cause death, along with significant risk reductions across multiple outcomes, including 16 percent for renal failure, 13 percent for congestive heart failure hospitalizations, 14 percent for major adverse cardiovascular events, 12 percent for stroke, 13 percent for non-fatal myocardial infarction and 14 percent for cardiovascular death.[7] Recognition of the role GLP-1 RAs play in systemic health has been reflected in clinical guidelines, with GLP-1 RAs recommended as first-line in the pharmacologic management of type 2 diabetes by the American Diabetes Association for patients with various systemic co-morbidities.[8]

GLP-1 RAs and DR: What the data show

The CDC's Vision and Eye Health Surveillance System estimated that in 2021, there were 9.6 million people (26 percent of those with diabetes) living with diabetic retinopathy in the United States and among them, 1.84 million people (5 percent) living with vision-threatening diabetic retinopathy.[9] Many of these patients are currently using or will eventually use GLP-1 RAs. Pre-clinical studies have demonstrated mixed findings, including potential protective effects of GLP-1 RAs in the context of diabetic retinopathy, with GLP-1 receptors found in the RPE serving a neuroprotective role in conditions of high glucose.[6]

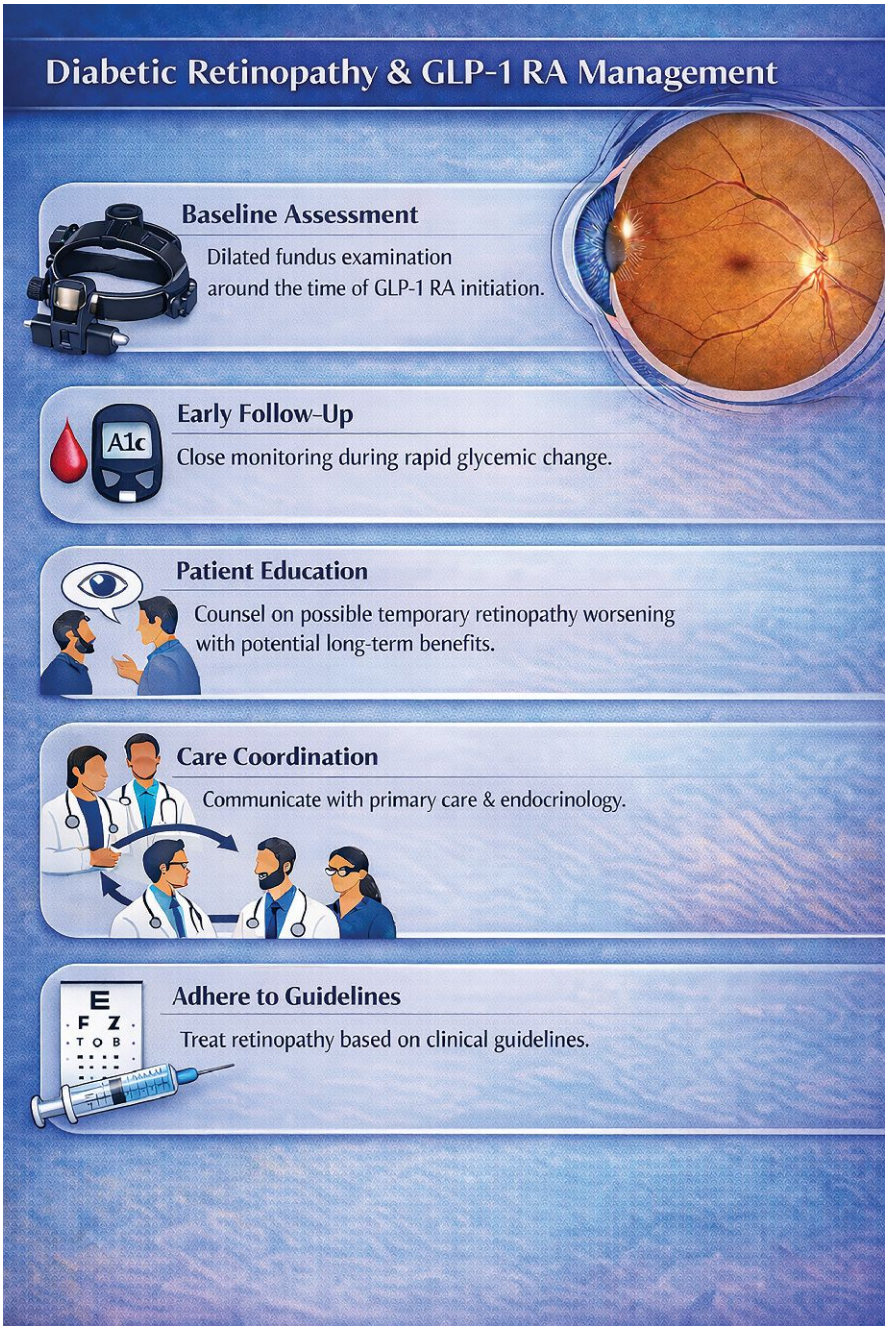
Yet in 2016, data from the SUSTAIN-6 trial comparing semaglutide to placebo over two years showed a possible increased risk of complications of diabetic retinopathy, including vitreous hemorrhage; the need for intravitreal injections and laser; and blindness (hazard ratio, 1.76; 95% CI, 1.11 to 2.78; p=0.02).[10] However, in the SUSTAIN-6 trial, there was also a significant drop in hemoglobin A1c (>1 percent) among participants receiving semaglutide during the first 16 weeks of GLP-1 RA therapy. The Diabetes Control and Complications Trial research group previously observed that early worsening of diabetic retinopathy can occur with intensive glycemic control, though effective glycemic control ultimately lowers retinopathy risk over the long-term.[11,12] The risk of complications in SUSTAIN-6 was highest among patients with pre-existing diabetic retinopathy and rapid HbA1c reduction, suggesting that the findings reflect the early worsening of diabetic retinopathy that can occur with any method of lowering glucose, rather than direct retinal toxicity from GLP-1 RAs.

Other trials of GLP-1 RAs have also not yet provided a clear answer. Most of the studies were designed to evaluate cardiovascular or renal outcomes, with diabetic retinopathy data collected through inconsistent and variably rigorous adverse events reporting. In 2004, researchers conducted a meta-analysis of 61 randomized controlled trials evaluating GLP-1 RAs, sodium-glucose co-transporter-2 inhibitors (SGLT2i), dipeptidyl peptidase 4 inhibitors (DPP-4i) and didn't find an increased risk of diabetic retinopathy events with GLP-1 RAs or any of the other classes of antihyperglycemic medications.[13]

Another study examined 93 trials and found an increased risk of diabetic retinopathy and retinal adverse effects with GLP-1 RA use, though this effect appeared driven by a single agent, albiglutide, which is no longer available.[14] Both studies were limited by relatively short follow-up among the included trials, narrow systemic in-

clusion criteria, limited information on baseline diabetic retinopathy status and, most important, inadequate and non-rigorous methodologies for diabetic retinopathy evaluation.[13,14]

Similarly, analysis of data from routine clinical practice has yielded varying results. One analysis used medical and pharmacy claims data to evaluate outcomes in 371,698 patients with type 2 diabetes initiating GLP-1 RA, SGLT2i, DPP-4i and sulfonylurea class medications, with the primary outcome being time-to-treatment for DME or PDR.[15] While the study showed a lower risk of sight-threatening retinopathy with SGLT2i, there was no increased risk with GLP-1 RAs compared with DPP-4i or sulfonylureas. Similarly, another study found a higher rate of progression of proliferative diabetic retinopathy as well as risk of new-onset diabetic macular edema with GLP-1 RAs compared to SGLT-2is.[16] However, a separate study didn't find a significant difference in clinical worsening of retinopathy or in need for intervention between GLP-1 RAs and SGLT-2i's.[17] Similarly, a group from Taiwan analyzed data from the Taiwan National Health Insurance Research Database and ultimately didn't find an increased risk of vision-threatening retinopathy with GLP-1 RA use and a possible decreased risk compared to DPP-4i.[18]



Just as there are differences between the antihyperglycemic agents, there are inter-agent differences between the GLP-1 RAs, with established differences in their glucose-lowering, lipid-lowering and weight loss effects. However, a study that performed three-way (exenatide vs. dulaglutide vs. liraglutide) and two-way (semaglutide vs. dulaglutide) comparisons among 125,336 adults with type 2 diabetes initiating a GLP-1 RA and found no difference in the rate of sight-threatening diabetic retinopathy between the different GLP-1 RA agents.[19] One report compared semaglutide with other GLP-1 RAs (dulaglutide, exenati-

de) and with non-GLP-1 RA antihyperglycemics (SGLT-2i, DPP4i, sulfonylurea).[20] The researchers didn't find an increased risk for proliferative diabetic retinopathy or for diabetic retinopathy/diabetic macular edema requiring treatment with semaglutide compared to the other GLP-1 RAs or to the non-GLP-1 RA antihyperglycemic medications.

While the studies published to date have limitations, there are several ongoing investigations, including the pivotal FOCUS trial, conducted as a post-authorization safety commitment to the European Medicines Agency.[21] The study has recruited 1,500 patients at 176 sites worldwide and compares semaglutide versus placebo in patients with type 2 diabetes. The primary outcome will be the percentage of participants with ≥3 step Early Treatment Diabetic Retinopathy Study (ETDRS) subject-level progression at five years, as well as secondary outcomes including 17 ocular and four systemic outcomes. The study will conclude in 2027 with results anticipated in early 2028.

In the meantime, retina specialists can counsel patients and the interdisciplinary care team that the data published to date haven't demonstrated definitive evidence of harm or an increased risk of diabetic retinopathy progression or vision-threatening adverse events with GLP-1 RA initiation. The principles of managing diabetic retinopathy remain unchanged in patients receiving a GLP-1 RA.

What to watch for and how to manage

If a patient presents with suspected issues with a GLP-1 RA drug, here's how to approach them:

• ***Baseline assessment.*** Baseline evaluation with dilated fundus examination prior to or shortly after GLP-1 RA initiation is recommended, particularly in patients with more advanced diabetic retinopathy. This helps clinicians determine how closely to follow patients after GLP-1 RA initiation as they may be at increased short-term risk.

• ***Early follow-up during glycemic change.*** Patients with diabetes who are initiating GLP-1 RAs—especially those with elevated baseline hemoglobin A1c or anticipated rapid reduction—may benefit from being monitored more closely than suggested by the American Academy of Ophthalmology preferred practice pattern, which is based on the current level of retinopathy. This mirrors management strategies used in other scenarios with significant anticipated glycemic change, such as pregnancy, intensive insulin therapy or bariatric surgery.

• ***Patient counseling and education.*** Patients should be counseled ahead of time that transient worsening of diabetic retinopathy or macular edema can happen whenever there is rapid glucose improvement, but that there are significant long-term benefits for diabetic retinopathy. Temporary worsening after GLP-1 RA initiation doesn't necessarily imply that GLP-1 RAs are harmful to the eye or should be discontinued. Setting expectations eases anxiety, improves adherence and reduces unnecessary discontinuation of therapy.

• ***Coordination with prescribing clinicians.*** Communication with the patient's care team, including primary care providers and endocrinologists, is essential. Management of diabetic retinopathy requires concurrent management of diabetes and other systemic parameters.

• ***Treatment of diabetic retinopathy according to established clinical guidelines.*** Management of diabetic retinopathy should follow established clinical guidelines and practice patterns, including anti-VEGF therapy, laser or surgery as indicated.

Conclusions

Ultimately, while further investigation will help clarify the risks and benefits of GLP-1 RAs with respect to diabetic retinopathy and vision-threatening complications, it's clear that GLP-1 RAs confer proven mortality and cardiovascular bene-

fit. There's currently no convincing evidence for avoiding or delaying GLP-1 RAs out of concern for diabetic retinopathy progression. There is, however, evidence to support considering closer follow-up when initiating a GLP-1 RA, particularly if rapid improvement in glycemic control is anticipated, following a baseline dilated fundus examination performed around the time of therapy initiation. Patients should be counseled that close follow-up is recommended and that there can be temporary worsening of diabetic retinopathy and diabetic macular edema with rapid intensive glycemic control. As GLP-1 RAs become increasingly prevalent, retina specialists play a critical role in ensuring that patients receive the systemic benefits of these agents while minimizing ocular risk through surveillance, education and collaboration.

REFERENCES

1. Vahratian A, Warren A. GLP-1 injectable use among adults with diagnosed diabetes: United States, 2024. NCHS Data Brief 2024;537:1-8.
2. Hegland TA, Fang Z, Bucher K. GLP-1 Medication use for type 2 diabetes has soared. JAMA 2024;332:12:952-953.
3. Doyle ME, Egan JM. Mechanisms of action of glucagon-like peptide 1 in the pancreas. Pharmacol Ther 2007;113:3:546-93.
4. Zhao X, Wang M, Wen Z, et al. GLP-1 receptor agonists: Beyond their pancreatic effects. Front Endocrinol (Lausanne) 2021;12:721135.
5. Puddu A, Sanguineti R, Montecucco F, Viviani GL. Retinal pigment epithelial cells express a functional receptor for glucagon-like peptide-1 (GLP-1). Mediators Inflamm 2013;2013:975032.
6. Zhou HR, Ma XF, Lin WJ, et al. Neuroprotective role of GLP-1 analog for retinal ganglion cells via PINK1/Parkin-Mediated Mitophagy in diabetic retinopathy. Front Pharmacol 2020;11:589114.
7. Badve SV, Bilal A, Lee MMY, et al. Effects of GLP-1 receptor agonists on kidney and cardiovascular disease outcomes: A meta-analysis of randomised controlled trials. Lancet Diabetes Endocrinol 2025;13:1:15-28.
8. American Diabetes Association professional practice committee for diabetes. pharmacologic approaches to glycemic treatment: Standards of care in diabetes—2026. Diabetes Care 2026;49:S183-S215.
9. Lundeen EA, Burke-Conte Z, Rein DB, et al. Prevalence of diabetic retinopathy in the US in 2021. JAMA Ophthalmol 2023;141:8:747-754.
10. Marso SP, Bain SC, Consoli A, et al. Semaglutide and cardiovascular outcomes in patients with Type 2 Diabetes. N Engl J Med 2016;375:19:1834-1844.
11. Diabetes C, Complications Trial Research G, Nathan DM, et al. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. N Engl J Med 1993;329:14:977-86.
12. Early worsening of diabetic retinopathy in the Diabetes Control and Complications Trial. Arch Ophthalmol 1998;116:7:874-86.
13. Malyszczak A, Przezdziecka-Dolyk J, Szydelko-Pasko U, Misiuk-Hojlo M. Novel antidiabetic drugs and the risk of diabetic retinopathy: A systematic review and meta-analysis of randomized controlled trials. J Clin Med 2024;13:6.
14. Kapoor I, Sarvepalli SM, D'Alessio D, Grewal DS, Hadziahmetovic M. GLP-1 receptor agonists and diabetic retinopathy: A meta-analysis of randomized clinical trials. Surv Ophthalmol 2023;68:6:1071-1083.
15. Barkmeier AJ, Herrin J, Swarna KS, et al. Comparative effectiveness of glucagon-like peptide-1 receptor agonists, sodium-glucose cotransporter 2 inhibitors, dipeptidyl peptidase-4 inhibitors, and sulfonylureas for sight-threatening diabetic retinopathy. Ophthalmol Retina 2024;8:10:943-952.
16. Wai KM, Mishra K, Koo E, et al. Impact of GLP-1 agonists and SGLT-2 inhibitors on diabetic retinopathy progression: An aggregated electronic health record data study. Am J Ophthalmol 2024;265:39-47.
17. Joo JH, Sharma N, Shaia J, et al. The effect of glucagon-like peptide-1 receptor agonists on diabetic retinopathy at a tertiary care center. Ophthalmol Sci 2024;4:6:100547.
18. Yen FS, Wei JC, Shih YH, et al. Glucagon-like peptide-1 receptor agonists and risk of sight-threatening retinopathy in Taiwanese population: A propensity based cohort study. Diabetes Metab Syndr 2024;18:8:103099.
19. Barkmeier AJ, Deng Y, Swarna KS, et al. Risk of sight-threatening diabetic retinopathy with glucagon-like peptide-1 receptor agonist use in routine clinical practice: Comparative effectiveness of semaglutide, dulaglutide, liraglutide, and exenatide. Ophthalmol Retina 2025. August 6, 2025:S2468-6530(25)00355-0. Online ahead of print.
20. Cai CX, Nishimura A, Baxter S, et al. Semaglutide and diabetic retinopathy: An OHDSI network study. BMJ Open Diabetes Res Care 2025;13:6.
21. A Research Study to Look at How Semaglutide Compared to Placebo Affects Diabetic Eye Disease in People With Type 2 Diabetes (FOCUS). NCT03811561. ClinicalTrials.gov.

(Continued from p. 15)

compromising vision."[22]

Satisfactory outcomes can be achieved by cautious tolerance of some residual, stable SRF. This approach allows patients to be treated using fewer injections, as suggested in the FLUID trial, where even small increases in the interval make a large difference over the patient's long-term treatment and to the health-care burden.

REFERENCES

1. Lek JJ, Caruso E, Baglin EK, et al. Interpretation of subretinal fluid using OCT in intermediate age-related macular degeneration. Ophthalmol Retina 2018;2:792–802.
2. Hilely A, Au A, Freund KB, et al. Non-neovascular age-related macular degeneration with subretinal fluid. Br J Ophthalmol 2021;105:1415–20
3. Madjarov B, Rosenfeld PJ. Serous PEDs with associated subretinal fluid unresponsive to anti-VEGF therapy. Invest Ophthalmol Vis Sci 2009;50:238
4. Sikorski BL, Bukowska D, Kaluzny JJ, Szkulmo-wski M, Kowalczyk A, Wojtkowski M. Drusen with accompanying fluid underneath the sensory retina. Ophthalmology 2011;118:82–92.
5. Adrean SD, Chaili S, Pirouz A, Grant S. Central serous chorioretinopathy in elderly patients mimicking occult neovascular age-related macular degeneration. Clin Ophthalmol 2020;14:4073–8.
6. Arrigo A, Aragona E, Battaglia Parodi M, Bandello F. Quantitative multimodal imaging characterization of intraretinal cysts versus degenerative pseudocysts in neovascular age-related macular degeneration. Ophthalmol Retina 2024;8:1118.
7. Ritter M, Simader C, Bolz M, et al. Intraretinal cysts are the most relevant prognostic biomarker in neovascular age-related macular degeneration independent of the therapeutic strategy. Br J Ophthalmol 2014;98:1629–35.
8. Waldstein SM, Wright J, Warburton J, Margaron P, Simader C, Schmidt-Erfurth U. Predictive value of retinal morphology for visual acuity outcomes of different ranibizumab treatment regimens for neovascular AMD. Ophthalmology 2016;123:60–9.
9. Waldstein SM, Simader C, Staurenghi G, et al. Morphology and visual acuity in aflibercept and ranibizumab therapy for neovascular age-related macular degeneration in the VIEW trials. Ophthalmology 2016;123:1521–9.
10. Sadda SR, Tuomi LL, Ding B, Fung AE, Hopkins JJ. Macular atrophy in the HARBOR study for neo-ascular age-related macular degeneration. Ophthalmology 2018;125:878–86.
11. Jaffe GJ, Ying GS, Toth CA, et al. Macular morphology and visual acuity in year five of the comparison of age-related macular degeneration treatments trials. Ophthalmology 2019;126:252–60.
12. Guymer RH, Rosenfeld PJ, Curcio CA, et al. Incomplete retinal pigment epithelial and outer retinal atrophy in age-related macular degeneration: Classification of Atrophy Meeting Report 4. Ophthalmology 2020;127:394-409.
13. Bailey C, Scott LJ, Rogers CA, et al. Intralesional macular atrophy in anti-vascular endothelial growth factor therapy for age-related macular degeneration in the IVAN trial. Ophthalmology 2019;126:75–86.
14. Sánchez-Monroy J, Nguyen V, Puzo M, et al. Sub-retinal fluid may protect against macular atrophy in neovascular age-related macular degeneration: 5 years of follow-up from Fight Retinal Blindness registry. Acta Ophthalmol 2023;101:457–64.
15. Llorente-González S, Hernandez M, González-Zamora J, et al. The role of retinal fluid location in atrophy and fibrosis evolution of patients with neovascular age-related macular degeneration long-term treated in real world. Acta Ophthalmol 2022;100:e521–31.
16. Rofagha S, Bhisitkul RB, Boyer DS, et al. Seven-year outcomes in ranibizumab-treated patients in ANCHOR, MARINA, and HORIZON: A multicenter cohort study (SEVEN-UP). Ophthalmology 2013;120:2292–99.
17. Guymer RH, Markey CM, McAllister IL, et al. Tolerating subretinal fluid in neovascular age-related macular degeneration treated with ranibizumab using a treat-and-extend regimen: FLUID study 24-month results. Ophthalmology 2019;126:723–34.
18. Hahn P, Eliott D, eds. 2021 Global Trends in Retina Survey [online]. 2021. https://www.asrs.org/content/documents/2021-global-trends-survey-highlights.pdf
19. Schmidt-Erfurth U, Chong V, Loewenstein A, et al. Guidelines for the management of neovascular age-related macular degeneration by the European Society of Retina Specialists (EURETINA). Br J Ophthalmol 2014;98:1144–67.
20. Flaxel CJ, Adelman RA, Bailey ST, et al. Age-Related Macular Degeneration Preferred Practice Pattern. Ophthalmology 2020;127:PP1–P65.
21. Chakravarthy U, Williams M, AMD Guidelines Group. The Royal College of Ophthalmologists Guidelines on AMD: Executive Summary. Eye 2013;27:1429–31.
22. Zur D, Guymer R, Korobelnik JF, Wu L, Viola F, Eter N, Baillif S, Chen Y, Arnold JJ. Impact of residual retinal fluid on treatment outcomes in neovascular age-related macular degeneration. British Journal of Ophthalmology 2025;109:3:307-15.

How to treat combined retinal detachment and macular hole

Understanding pathologies, traction removal, ILM flap and how to improve outcomes.

By Masaki Fukushima, MD, Akihiko Shiraki, MD, Taku Wakabayashi, MD, PhD

Take-home points

- Combined retinal detachment and macular hole can be classified into two different clinical conditions: macular hole retinal detachment in highly myopic eyes, which we'll discuss in this article; and primary rhegmatogenous RD with a concurrent (non-causal) macular hole in non-highly myopic eyes.
- MHRD in highly myopic eyes typically results from tangential traction due to the adherent vitreous cortex, epiretinal membrane and internal limiting membrane, as well as anteroposterior traction associated with posterior staphyloma and reduced retina/retinal pigment epithelium adhesion. The goal of surgery is to remove the traction to the greatest extent possible by removing any vitreous cortex remnants, ERM and ILM, thereby achieving MH closure and retinal reattachment.
- The current standard techniques include pars plana vitrectomy, removal of vitreous cortex and ERM, an inverted ILM flap and long-acting gas tamponade. Refractory MHRD may benefit from alternative techniques, such as autologous retinal transplantation, human amniotic membrane transplantation and macular buckle.


Masaki Fukushima, MD Akihiko Shiraki, MD

Taku Wakabayashi, MD, PhD

The prevalence of high myopia is rising worldwide, predicted to increase by nearly 9.8 percent (approximately 1 billion people) globally by 2050.[1] This trend suggests that the vision-threatening complications associated with high myopia, including macular hole retinal detachment, will become increasingly important.

MHRD is a retinal detachment associated with a full-thickness macular hole. It occurs predominantly in highly myopic eyes with posterior staphyloma, but its pathogenesis differs from that of primary rhegmatogenous RD associated with concurrent MH in non-highly myopic eyes. The pathogenesis of MHRD is multifactorial, involving tangential traction from the vitreous cortex and epiretinal membrane,[2] anteroposterior traction associated with posterior staphyloma[3] and reduced adhesion between the retina and retinal pigment epithelium due to myopic maculopathy (chorioretinal atrophy).[3] Both tangential and anteroposterior traction promote MH formation, which is followed by the entry of subretinal fluid through the hole and progression to MHRD. Because these tractional forces constitute the underlying pathology, the goals of surgery are to relieve this traction, achieve MH closure and reattach the retina.

Our surgical techniques

Here are our strategies and important considerations for each step of MHRD repair:

• ***Incision***. We perform pars plana vitrectomy with an inverted ILM flap and long-acting gas tamponade as our first-line technique for MHRD *(Figure 1; video at: http://bit.ly/4rrP8eb)*. In highly myopic eyes, standard sclerotomy sites (3.5 to 4 mm) may not allow forceps to reach the macula because of the long axial length. The distance from the limbus to the ora serrata is greater in highly myopic eyes than in non-myopic eyes and commonly exceeds 5 mm in eyes with an axial length over 27 mm.[4] There-

BIOS

Dr. Masaki Fukushima is a vitreoretinal surgeon at Kindai University and the University of Toyama, Japan.

Dr. Akihiko Shiraki is a vitreoretinal surgeon at Osaka University, Japan.

Dr. Taku Wakabayashi is a vitreoretinal surgeon at Wakabayashi Eye Center and a clinical professor of ophthalmology at Kanazawa University, Japan.

Disclosures: The authors have no relevant financial disclosures.

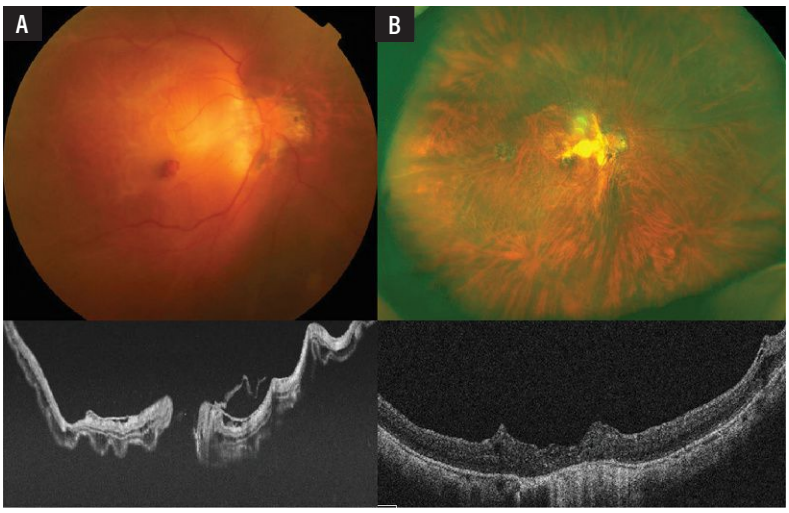


Figure 1. Preoperative and postoperative images of a patient with macular hole retinal detachment in a highly myopic eye. (A) Preoperative fundus photograph and OCT show MHRD. The axial length was 30.9 mm. (B) Postoperative images demonstrate successful macular hole closure and retinal reattachment after vitrectomy, ILM flap and 10 percent C3F8 tamponade. The vision improved from 20/1000 to 20/100.

fore, creating sclerotomies more posteriorly (approximately 5 mm from the limbus) helps in reaching the macula.

Another helpful technique is to first create a standard sclerotomy on the nondominant (e.g., left hand) side and then insert the light pipe into the vitreous cavity to identify the ora serrata on the dominant (e.g., right hand) side by observing transillumination from within the eye. Because the retina and pars plana differ in their light-transmission characteristics, the boundary between them can be clearly distinguished *(View the video:* https://bit.ly/4sG5wIY). Direct visualization of the ora serrata with scleral indentation is another useful technique for safe entry.

• ***Long-shafted instruments***. Preoperative measurement of the axial length is useful for determining whether standard forceps will suffice or long-shafted instruments are required. In eyes with an axial length greater than 32 mm, long-shafted forceps may be an option. Alternative approaches include temporarily lowering the infusion pressure or removing the cannula to gain further distance.

• ***Vitreous cortex removal.*** Since the vitreous plays a key role in the pathogenesis of MHRD,[5] complete separation of the posterior hyaloid and removal of vitreous cortex remnants and ERMs are essential for successful retinal reattachment. As first described by Drs. Stirpe and Michels,[2] even in eyes with posterior vitreous detachment, vitreoschisis very commonly occurs in highly myopic eyes, often leaving residual vitreous cortex remnants and ERMs adhered to the posterior pole and beyond. Triamcinolone acetonide should be used routinely to assess the status of PVD and visualize the vitreous cortex remnants and ERMs. Repeated triamcinolone staining, combined with the use of forceps, a diamond-dusted membrane scraper (Tano scraper, Bausch + Lomb) or a Finesse Flex Loop (Alcon), facilitates the efficient removal of the vitreous cortex from the posterior pole.

In eyes with a highly elevated detached retina, these maneuvers can be challenging. In such cases, drainage of subretinal fluid through the preexisting MH may help flatten the retina and improve manipulation. However, SRF should be gently aspirated, as active drainage may enlarge the MH and cause additional foveal damage.

• ***Internal limiting membrane staining and flap***. Complete removal of the multilayered vitreous cortex improves subsequent ILM staining with Brilliant Blue G and indocyanine green. After we stain the ILM, we create a multilayer inverted ILM flap to cover the hole. Since hole closure rates are around 40 percent after conventional complete ILM peeling, we routinely use an ILM flap to improve the hole closure. A multilayer flap provides more reliable coverage than a single-layer flap, particularly in large MHs. Viscoelastic is a useful material for stabilizing the inverted flap over the hole. The remaining ILM not used for the flap is broadly peeled, ideally extending from arcade to arcade.

Whether the ILM flap should be covered or inserted into the hole remains controversial. We use the cover technique for small-to-medium-sized holes that show less extensive SRF. However, flap displacement may oc-

casionally occur during fluid-air exchange or in the postoperative period, resulting in persistent macular hole opening. For this reason, an insertion technique is often preferred, especially in large MHs and cases with extensive SRF, as this provides greater flap stability, even during fluid-air exchange.[6] The potential disadvantage of an insertion technique is the formation of a glial scar at the fovea; however, hole closure is prioritized in cases with MHRD caused by large MH.

Several technical approaches can be considered when creating ILM flaps in eyes with MHRD. The inverted ILM flap can be performed under fluid without the use of perfluorocarbon liquid. In cases of MHRD within the posterior pole, SRF drainage is unnecessary when performing ILM flaps. In eyes with highly elevated detached retinas, gentle aspiration of SRF through the hole reduces the retinal height and aids in flap manipulation. Avoiding PFCL allows easier forceps access to the macula, as the detached retina rises anteriorly and shortens the working distance; however, flap stability may be reduced. Therefore, PFCL can be used to flatten the retina and provide better control when positioning the inverted ILM flap. In cases of inadequate ILM staining, restaining with the dye under PFCL can also be effective *(Video available at:* https://bit.ly/4sG5wIY*)*. The potential disadvantage of using PFCL is the increased distance between the sclerotomy site and the macula, although long-shafted forceps can overcome this limitation.

• ***Fluid-air exchange***. After peripheral vitreous shaving, we perform fluid-air exchange. During this exchange, the SRF can usually be left in place, especially when the RD is limited to the posterior pole or can be drained through a drainage retinotomy that's created outside the vascular arcade in cases of extensive RD. The SRF can also be aspirated through the original MH; however, this carries the risk of hole enlargement and may cause RPE damage from the soft-tip cannula. Therefore, we don't recommend complete SRF aspiration through the MH. Successful retinal reattachment can be achieved even without complete fluid removal.

• ***Tamponade***. The most commonly used long-acting gas tamponades include 20 percent SF6 or 10 percent C3F8 gas, with one study showing comparable outcomes between the two.[7] Another study reported higher retinal reattachment rates with gas compared with silicone oil, although the MH closure rates and final visual acuity didn't differ significantly between the two groups.[8] Nevertheless, silicone oil tamponade remains an effective option, especially in only one seeing eye (relatively common in severe pathologic myopia) or in cases of recurrence or proliferative vitreoretinopathy that require prolonged tamponade.

• ***Macular buckle and other techniques***. Although most MHRDs can be successfully managed with PPV alone, recurrent MHRD may require alternative techniques, such as human amniotic membrane transplantation or autologous retinal transplantation.[9,10] In some cases, macular buckle is also

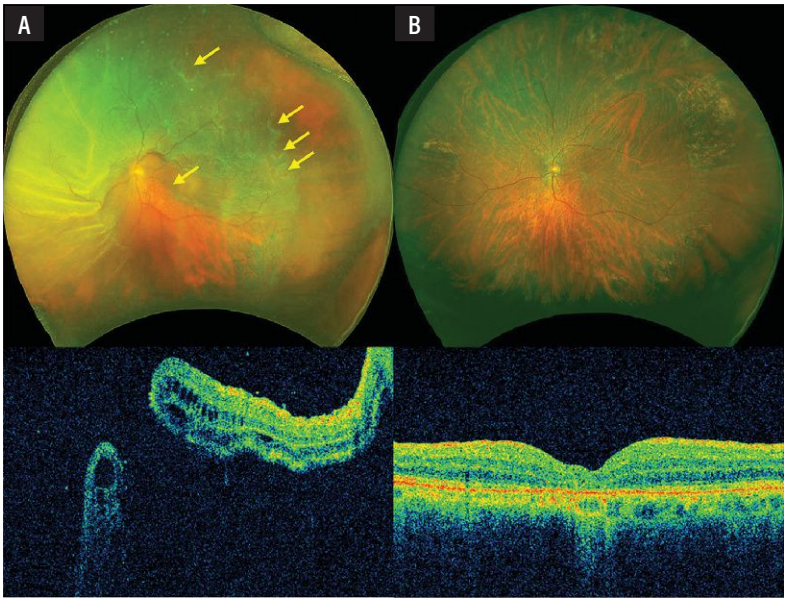


Figure 2. Preoperative and postoperative images of a patient with primary rhegmatogenous retinal detachment and concurrent macular hole a in non-highly myopic eye. (A) Preoperative fundus photograph and OCT show multiple peripheral breaks and concurrent macular hole (yellow arrows). The axial length was 24.5 mm. (B) Postoperative images demonstrate successful macular hole closure and retinal reattachment after vitrectomy, ILM peeling and 20 percent SF6 gas tamponade. The vision improved from 20/1000 to 20/200.

effective for recurrent MHRD despite prior vitrectomy with ILM peeling and tamponade, as the procedure relieves anteroposterior traction by indenting the posterior pole and counteracting the deforming forces of the posterior staphyloma.[11,12]

Surgical outcomes

A recent meta-analysis indicates that hole closure rates are around 40 percent after vitrectomy with complete ILM peeling, 94.3 percent with the ILM flap covering and 91.6 percent with the ILM flap insertion technique.[13] The reattachment rates are 69 percent to 100 percent after complete ILM peeling, 91.8 percent after ILM flap covering and 97.1 percent after the ILM flap insertion.[13] The hole closure is an important factor for retinal reattachment, and using an ILM flap increases the likelihood of positive anatomic outcomes. Visual improvement can be achieved in more than 80 percent of eyes treated with the inverted ILM flap.[13] However, the mean visual acuity after vitrectomy is often lower than 20/200.[14] A longer axial length is generally a poor prognostic factor.

Recurrent RD and PVR are major postoperative complications after vitrectomy for MHRD. Identification and removal of residual vitreous cortex, ERMs and any remaining ILM are critical during reoperation. However, the cause of redetachment is sometimes difficult to identify. In those cases, the responsible factors may be persistent traction due to posterior staphyloma and underlying severe chorioretinal atrophy. For cases with these issues, surgeons may consider alternatives, such as macular buckle, human amniotic membrane transplantation and autologous retinal transplantation.

Rhegmatogenous RD with concurrent MH

In primary RRD with concurrent MH in non-highly myopic eyes, the detachment is caused by peripheral retinal breaks, whereas the MH is a coexisting rather than causative lesion *(Figure 2)*. Surgical management includes PPV, peripheral vitreous shaving and intraocular tamponade. ILM peeling may be performed to facilitate MH closure; however, an inverted ILM flap may also be considered in large MHs. Anatomic outcomes are similar between RRD with and without concurrent MH; however, visual outcomes are worse in eyes with concurrent MH.[15]

Conclusion

PPV, ILM flap and long-acting gas tamponade are the mainstays of treatment for MHRD in highly myopic eyes. However, surgical techniques should be individualized, as the MH size, extent of RD, severity of myopic maculopathy and presence or absence of PVR may vary in each case, resulting in varied surgical approaches. A thorough understanding of the underlying pathologies and optimal surgical techniques is essential for improving long-term anatomic and visual outcomes in this challenging condition. RS

REFERENCES

1. Holden BA, Fricke TR, Wilson DA, et al. Global prevalence of myopia and high myopia and temporal trends from 2000 through 2050. Ophthalmology 2016;123:5:1036-1042.
2. Stirpe M, Michels RG. Retinal detachment in highly myopic eyes due to macular holes and epiretinal traction. Retina 1990;10:2:113-114.
3. Morita H, Ideta H, Ito K, et al. Causative factors of retinal detachment in macular holes. Retina 1991;11:3:281-284.
4. Hirono K, Inoue M, Tanaka S, et al. Anterior segment optical coherence tomography in determination of entry site for vitrectomy in highly myopic eyes. Retina 2023;43:5:733-738.
5. Gonvers M, Machemer R. A new approach to treating retinal detachment with macular hole. Am J Ophthalmol 1982;94:4:468-472.
6. Chen SN, Yang CM. Inverted internal limiting membrane insertion for macular hole-associated retinal detachment in high myopia. Am J Ophthalmol 2016;162:99-106.e1.
7. Nakanishi H, Kuriyama S, Saito I, et al. Prognostic factor analysis in pars plana vitrectomy for retinal detachment attributable to macular hole in high myopia: A multicenter study. Am J Ophthalmol 2008;146:2:198-204.
8. Kakinoki M, Araki T, Iwasaki M, et al. Surgical outcomes of vitrectomy for macular hole retinal detachment in highly myopic eyes a multicenter study. Ophthalmol Retina 2019;3:10:874-878.
9. Caporossi T, Angelis LD, Pacini B, et al. A human amniotic membrane plug to manage high myopic macular hole associated with retinal detachment. Acta Ophthalmol 2020;98:2:e252-256.
10. Moysidis SN, Koulisis N, Adrean SD, et al. Autologous retinal transplantation for primary and refractory macular holes and macular hole retinal detachments—The Global Consortium. Ophthalmology 2021;128:5:672-685.
11. Ge JY, Teo AWJ, Tsai ASH, et al. Macular buckle, vitrectomy or combined approach for the management of macular hole retinal detachment: A systematic review and network meta-analysis. Ophthalmol Retina 2025; doi:10.1016/j.oret.2025.08.020.
12. Ripandelli G, Coppé AM, Fedeli R, et al. Evaluation of primary surgical procedures for retinal detachment with macular hole in highly myopic eyes: A randomized comparison of vitrectomy versus posterior episcleral buckling surgery. Ophthalmology 2001;108:12:2258-2264.
13. Chatziralli I, Machairoudia G, Kazantzis D, Theodossiadis G, Theodossiadis P. Inverted internal limiting membrane flap technique for myopic macular hole: A meta-analysis. Surv Ophthalmol 2021;66:5:771-780.
14. Wakabayashi T, Ikuno Y, Shiraki N, et al. Inverted internal limiting membrane insertion versus standard internal limiting membrane peeling for macular hole retinal detachment in high myopia: One-year study. Graefes Arch Clin Exp Ophthalmol 2018;256:8:1387-1393.
15. Starr MR, Obeid A, Ryan EH, et al. Surgical outcomes of primary RRD with and without concurrent full-thickness macular hole (PRO Study Report No. 7). Ophthalmic Surg Lasers Imaging Retina 2020;51:9:500-505.

Managing hyperacute epiretinal membranes

Expert guidance on selecting interventions for optimal visual outcomes.

By Justin Muste, MD, Sunir Garg, MD, and Jason Hsu, MD

Take-home points

- Hyperacute epiretinal membranes are those that develop within the first three months after a retinal detachment but the ERMs aren't always visually significant.
- Up to a third of eyes with horseshoe tears (HST) that require laser retinopexy (LR) develop ERM requiring surgery within six months.
- Timing matters: Internal limiting membrane peeling within six months of rhegmatogenous retinal detachment repair yields significantly better visual outcomes (20/40) compared to surgery performed beyond six months (20/80).
- While prophylactic ILM peeling during primary RD repair reduces ERM formation (from 29 to 46 percent to 1.8 to 3 percent), final visual outcomes remain similar between groups.
- However, high-risk patients—those with preoperative vitreous hemorrhage, extensive cryotherapy or visible retinal surface wrinkling during initial surgery—may benefit from prophylactic ILM peeling.

Despite advances in vitreoretinal surgical techniques, secondary epiretinal membrane formation occurs after retinal tears as well as after rhegmatogenous retinal detachment. After retinal tears, ERM occurs in 2.9 to 31.7 percent of patients. After RRD, the incidence ranges from 4.6 percent to as high as 49 to 70.3 percent depending on detection methods, patient characteristics and follow-up duration.[1-4] Thankfully, not all ERMs are visually significant.[4]

A clinically significant subset of epiretinal membranes develop rapidly in the early postoperative period, leading to metamorphopsia, decreased visual acuity and patient dissatisfaction despite successful retinal detachment repair.

The challenge for retinal surgeons lies in identifying which patients will develop problematic membranes and determining the optimal timing for surgical intervention in these cases.

When do hyperacute ERMs develop?

The term "hyperacute" distinguishes rapidly forming postoperative ERMs from more indolent idiopathic membranes. A hyperacute membrane develops within the first three months following repair, with approximately 90 percent of ERMs following RD appearing during this window.[1,5]

Ishida and colleagues performed systematic optical coherence tomography surveillance of 322 eyes at one, three, six and 12 months after retinal detachment repair. Of the 39 eyes that developed an ERM over the 12-month follow-up period, 13 eyes (33.3 percent) developed an ERM by one month, 30 eyes had an ERM at 3 months (77 percent) and 36 eyes had an ERM at six months (92.3 percent). Notably the study was anatomic in scope and visual significance wasn't discussed; most likely many of these ERMs weren't visually significant.

There's less literature addressing ERM that occurs after laser retinopexy for horse-

Justin Muste, MD

Sunir Garg, MD

Jason Hsu, MD

BIOS

Dr. Muste is a vitreoretinal surgical fellow at Wills Eye Hospital in Philadelphia.

Dr. Garg is a professor of Ophthalmology on the Retina Service at Wills Eye Hospital and Thomas Jefferson University, and a partner at Mid Atlantic Retina. He also serves as co-director of the Retina Research Unit at Wills.

Dr. Hsu is a faculty member of the Retina Service at Wills Eye Hospital and professor of ophthalmology at the Sidney Kimmel Medical College of Thomas Jefferson University. He serves as co-director of the Retina Research Unit at Wills.

shoe tear. Blackorby and colleagues showed 2.9 percent of eyes developed an ERM after LR. The average time to ERM development was 12 months after laser retinopexy (Range: 1.5 to 94 months).[6] In a series of clinical outcomes of HST after requiring LR, Choi and colleagues incidentally noted 7.4 percent of eyes developed an ERM at three months.[7] However, no single study specifically addresses hyperacute ERM following LR. As noted above, it's not clear how visually significant the ERMs are.

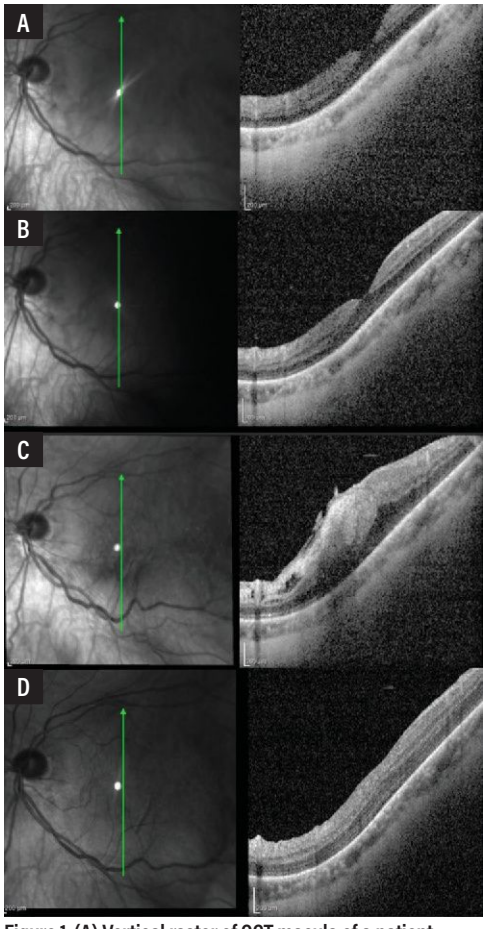


Figure 1. (A) Vertical raster of OCT macula of a patient presenting for a new HST with a visual acuity of 20/30. (B) Two weeks after laser retinopexy, the OCT macula remained unchanged and the visual acuity remained 20/30. (C) Five weeks after laser retinopexy, visual acuity declined to 20/100 with ERM formation. (D) The patient was taken for ILM peel with OCT two months after presentation. One month after surgery, there was restoration of foveal architecture. Although the patient reported improved vision quality, the vision recovery wasn't complete at this point, with vision at 20/350 and improving.

From our experience, visually significant ERM can form after any retinal break including HST alone *(Figure 1)* and RD *(Figure 2)* within 90 days. However, future studies are needed to characterize the timing and risk factors for membrane formation.

Why membranes form: Pathophysiology and Risk Factors

ERM derives from liberated retinal pigment epithelial cells undergoing transformation.[5,8] Factors such as larger or more numerous tears and more extensive RDs are associated with increased RPE cell liberation.

Hirakata and colleagues identified four perioperative risk factors that increase the odds of ERM formation: postoperative redetachment (OR 19.7; 95% CI [4.87–79.38], $p<0.01$), retinal detachment area >3 clock hours (OR 12.91; 95% CI [2.34–71.19] $p< 0.01$), more than three retinal breaks (OR 8.07; 95% CI [2.35–27.71],$p<0.01$) and preoperative vitreous hemorrhage (OR 4.71; 95% CI [1.19–18.62], $p=0.03$).[9] Other authors similarly underscore the importance of these risk factors, which may elevate inflammatory mediators and increase cellular proliferation.[1,5,8,9]

Intraoperative factors matter as well. For ERM in general, Szigiato and colleagues report laser photocoagulation exceeding 1,000 spots, choroidal detachment and 360-degree laser treatment all significantly increase ERM formation risk after PPV for RD repair.[8] The data around cryotherapy is mixed with some authors finding a significant association with ERM formation while others report no association.[8,9] Some authors suggest that initial macula-off status increases the likelihood of developing an ERM while others haven't found any association.[1,2,4,8]

Israelivich and colleagues examined 42 eyes that underwent ERM surgery after LR. They found 16 of 42 eyes (38.1 percent) that underwent surgery ≤180 days from LR were younger and more likely to have Stage 4 ERM characteristics with ectopic inner foveal layers and disorganized retinal layers.[10] Notably, the presence of VH at the time of laser, number of retinal tears and location of retinal tear weren't different in eyes the ≤180 days versus >180 day group. However, concurrent RD with a mean of 1.7 clock hours in size was more likely to result in earlier surgery for ERM. This is in line with the above discussion regarding liberated RPE as a driver of ERM formation.

Seeing Cellophane: OCT classification and staging

Spectral-domain OCT has fundamentally changed how we detect and characterize ERMs. Although the classification system developed by Govetto and colleagues was originally used for idiopathic membranes, it provides a standardized framework that can be used in hyperacute membranes as well.[11]

The classification progresses through four stages:

— Stage 1 membranes preserve the foveal depression with well-defined retinal layers.

— Stage 2 demonstrates loss of the foveal

pit while maintaining distinguishable retinal architecture.

— Stage 3 ERMs have EIFL in addition to Stage 2 features.

— Stage 4 ERM show EIFL with disrupted and disorganized retinal layers.[11]

Some authors report 65 to 67 percent of ERMs that occur within three months after RRD repair and LR reach Stage 4.[1,12] It's known that EIFL and disruption of outer retinal structures correlates with worse visual outcomes and persistent metamorphopsia. These findings raise the question of whether intervention before structural changes become irreversible is better than waiting for more vision loss to occur. However, these studies often select for eyes undergoing surgery for ERM repair. As such it's difficult to be certain what proportion of ERMs that present following RRD or LR will advance to Stage 4 when considering the whole population.

When to intervene?

Ultimately, this question is best resolved on a case-by-case basis. A visually significant cataract may need to be removed before or concurrent with PPV and membrane peeling for a visually significant ERM. Proceeding with combined surgery or staging is a separate area of discussion that we will save for a future article.

Regarding hyperacute ERM, there's some data that can guide management. Bomdica and colleagues report a series of 55 cases of ERM following RRD repair. The authors divided the group into 37 eyes undergoing PPV and ILM peel within six months and 18 eyes treated beyond six months. These groups achieved a final visual acuity of 20/40 and 20/80, respectively.[1] The authors suggest patients who had a membrane peel six months or later had cataract surgery prior to the PPV for the ERM and this was likely the cause for the delay. The authors suggest earlier intervention (within six months following RD occurrence as per their study design) may be beneficial. This fits with the pathophysiology and staging reviewed above. Presumably, the more time that an aggressive, rapidly progressive ERM can exert traction on the macula, the more likely macula dysfunction occurs.

We favor earlier intervention in these cases as anecdotally we seem to achieve better visual and anatomic outcomes *(Figures 1 and 2).*

PPV with ILM peel during the ERM surgery rather than ERM peel alone also seems to be better. Council and colleagues reported positive outcomes with no significant increase in recurrent retinal redetachment following ILM peel. It should be noted that 79.1 percent of the phakic patients in their study underwent subsequent phacoemulsification.[13] As such, all patients should be counseled about cataract formation after vitrectomy.

Following cataract surgery, patients may be advised of the risks of macular edema and macular hole formation. Mylonas and colleagues found higher rates of macular edema up to 42 percent following successful cataract surgery in eyes with PPV and ILM peel.[14] Though no study clearly tracks the rate of macular hole formation following cataract surgery in eyes with PPV and ILM peel, Rush and colleagues retrospectively reviewed 423 eyes after PPV and ILM peel. They found macular holes may form in 2.6 percent of cases.[15]

What about peeling at the time of initial RRD repair?

The rationale for ILM peeling prophylactically at the time of RRD is straightforward: If there's a risk for ERM formation, why not remove the scaffold on which membranes develop? ILM peeling during RD repair reduces postoperative ERM formation. A recent meta-analysis of 3,420 eyes found ILM peeling reduced

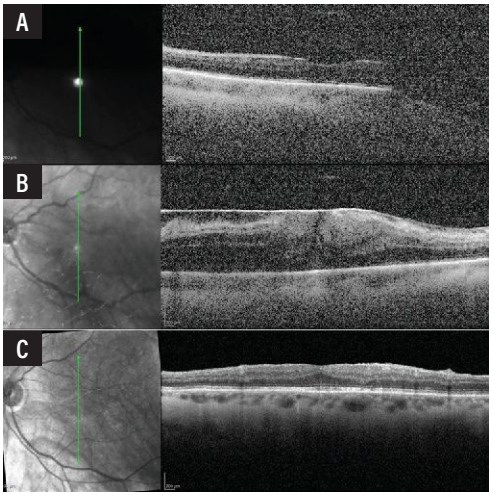


Figure 2. (A) Vertical raster of OCT macula of the left eye one month after pars plana vitrectomy for retinal detachment repair. Visual acuity was 20/150, an improvement from the presenting visual acuity of counting fingers. (B) Eight weeks after retinal detachment repair, an ERM had formed with the visual acuity declining to counting fingers. (C) The patient had an ILM peel 12 weeks after retinal detachment repair. One year following ILM peeling, the OCT continued to improve with reconstitution of foveal architecture with the visual acuity improving to 20/40.

ERM formation to 1.5 percent from 8.5 percent in the control group. However, no significant difference in mean visual acuity was noted between the two groups, suggesting that waiting for the ERM to occur and fixing it at that point is a reasonable option.[16]

As discussed above, not all ERMs are visually significant, and vitrectomy with membrane peel can lead to iatrogenic retinal breaks, inner retinal dimpling and retinal pits. These may be signs of Mueller cell trauma and correspond to microscotoma, which raises questions of subclinical effects of peeling.[17,18] One potential limitation of this study is that the final follow-up varies among studies and this may affect how authors appreciate final visual improvement. For example, Nam and colleagues observed eyes to 12 months after peeling and reported a better mean visual acuity in ILM peel patients.[19] Similarly, cataract management also varied between the studies and could have influenced rates.

Currently, we don't routinely peel ILM in eyes undergoing RRD repair. However, selective prophylaxis in high-risk cases is worth considering.

Currently, we don't routinely peel ILM in eyes undergoing RRD repair. However, selective prophylaxis in high-risk cases is worth considering. Patients with preoperative vitreous hemorrhage, extensive laser treatment (>1,000 spots) or preexisting retinal surface wrinkling during surgery may benefit most from prophylactic intervention.

What is the optimal management strategy?

We recommend a risk-stratified approach to managing hyperacute ERM after retinal tears with or without a history of RD repair.

- ***Routine-risk cases***. Implement surveillance with OCT imaging at one month and three months postoperatively to capture the peak window of ERM development. Most patients will not develop visually significant membranes that require intervention, but they should be counseled about doing monocular vision checks regularly.
- ***High-risk cases.*** Consider prophylactic ILM peeling during the primary repair. The appearance of retinal surface wrinkling deserves particular attention. Akiyama and colleagues found that specifically peeling eyes that had visible wrinkling prevented all visually significant postoperative ERMs, though this finding may reflect early PVR-B changes.[3,18]
- ***Symptomatic ERMs developing during surveillance***. Consider intervention within six months of RD/tear repair. Waiting for cataract maturation or adhering to arbitrary time intervals may be unnecessary and may compromise outcomes. Some eyes have profound ERM formation that looks and behaves like extensive PVR. In these instances, it may be prudent to perform MP early.
- ***Counsel phakic patients.*** Cataract surgery will likely be needed after vitrectomy.[13] In selected cases and certain localities, combined cataract surgery with membrane peeling may be preferred.
- ***Not everyone with an ERM needs surgery***. In Szigiato and colleagues's cohort, 58 percent of patients developed OCT-visible ERMs but only 5 percent ultimately required surgical intervention.[8] This underscores the importance of clinical correlation and patient symptoms rather than treating OCT findings alone.

What patients can expect: Outcomes and prognosis

Setting appropriate expectations is crucial. Visual prognosis following PPV with membrane peeling depends on multiple factors: membrane stage and duration, integrity of outer retinal structures and baseline visual potential.

From the literature regarding idiopathic ERMs, metamorphopsia persists in a substantial proportion of patients despite anatomic improvement, particularly in eyes with preoperative ectopic inner foveal layers.[11] While visual acuity typically improves following membrane peeling, some degree of distortion often remains. Patients should understand that symptomatic improvement may take months, and some metamorphopsia and blurriness can persist.

Council and colleagues's series of 79 eyes undergoing ERM peeling after RD repair

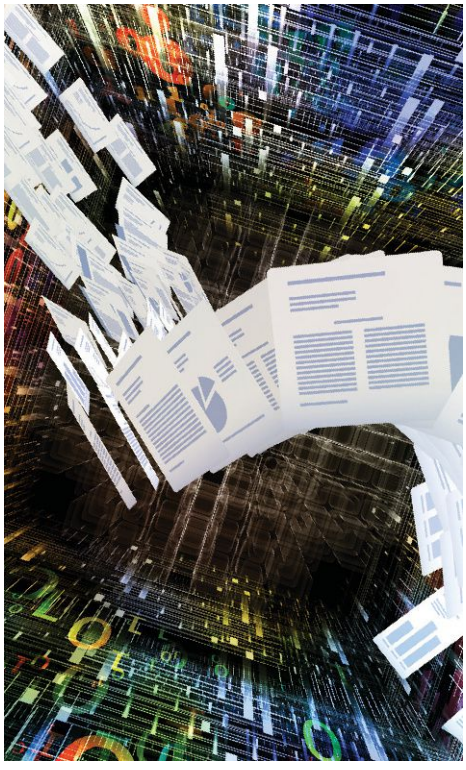
(Continued on p. 30)

From journals to feeds: The evolution of research dissemination

Peer review remains the gold standard for validation—but is no longer the sole driver of influence.

By Jayanth Sridhar, MD

For most of modern medicine and science, the pathway from discovery to dissemination has followed the same route: A study is conducted, a manuscript is written, and the work undergoes peer review before appearing in a scientific journal. This system has long served as the backbone of academic credibility. Peer review functions as a form of collective scrutiny: Methods are examined (and ideally reproduced by other groups), statistical analyses are questioned and conclusions are tempered before publication.



In principle, this process acts as a filter against flawed reasoning, overstated claims and methodological weaknesses. The result isn't perfect science, but science that has at least survived structured criticism from experts in the field.

Yet the pace of modern communication has shifted dramatically. Social media platforms now allow researchers to distribute ideas, figures and preliminary findings instantly to thousands of readers. In some cases, new data appear online within hours of being generated, bypassing months, or sometimes years, of editorial review.

For clinicians and trainees accustomed to the traditional cadence of academic publishing, this creates a strange hybrid environment. Moreover, for the new generation of rising doctors, social media dissemination may represent the norm rather than the exception. Important insights may circulate widely long before they appear in print, while established journals feel increasingly slow in comparison.

Peer review still provides several advantages that remain difficult to replicate elsewhere. Independent reviewers act as a quality control mechanism, forcing authors to defend their methodology, clarify assumptions and justify conclusions. Statistical errors, overlooked confounders, and interpretive overreach are frequently caught during this process.

Equally important is validation; publication in a peer-reviewed journal signals that the work has been evaluated by knowledgeable colleagues rather than simply amplified by an algorithm. In fields such as medicine, where claims can influence clinical practice and patient decision-making in an era of increasing patient autonomy, this gatekeeping func-

BIO

Dr. Sridhar is an associate professor of clinical ophthalmology at Bascom Palmer Eye Institute, Miami.

DISCLOSURES

Dr. Sridhar is a consultant to Alcon, DORC, Genentech/Roche and Regeneron Pharmaceuticals.

tion remains essential.

At the same time, the traditional system carries real drawbacks. The process is slow, expensive and often opaque. Journals rely heavily on unpaid labor from editors and peer reviewers, even as major publishers maintain substantial profit margins. Authors frequently pay article processing charges or page fees to publish within what many describe as the "academic rat race," and institutions pay again through journal subscriptions. Months of revision cycles can delay the communication of results that may already be circulating informally. Reviewers can be arbitrary and may bring their own biases against certain institutions or author groups. From the perspective of younger researchers navigating career timelines, the system can feel both inefficient and inequitable.

Social media occupies the opposite extreme. Information spreads rapidly, discussion occurs in real time, and a single well-designed figure can reach a global audience overnight. These platforms can democratize scientific conversation, allowing trainees, clinicians and researchers from outside traditional academic hierarchies to engage directly with new work.

However, speed comes at a cost. Without structured review, incorrect interpretations can propagate quickly, nuance may disappear and popularity can substitute for rigor. The result is a communication ecosystem where valuable insight must compete with the noise of premature conclusions.

Scientific discourse is therefore entering a transitional phase. Peer-reviewed journals remain the most reliable mechanism for validating research, but they no longer monopolize attention or influence. Social media accelerates discussion but can't fully replace structured evaluation.

The likely future isn't one system replacing the other, but an uneasy coexistence—rapid online conversation paired with slower, more deliberate validation. In that environment, the challenge for physicians and researchers will be learning how to move between both worlds, engaging with new ideas quickly while still demanding the rigor that good science requires. At the same time, journals and peer-reviewed publications may need to evolve their processes to remain relevant in a faster-moving scientific landscape.

(Continued from p. 28)

showed that 79 percent achieved visual acuity of 20/40 or better, though 21 percent had persistent vision of 20/50 or worse.[13] With this data in mind, it might be prudent to emphasize that membrane peeling aims to halt progression and improve symptoms rather than restore normal vision. Moreover, the original RRD may have already caused permanent changes that limit final visual potential regardless of subsequent membrane surgery.

Looking ahead

Although controlling for individual features of RRD and HST isn't easily done, there are opportunities for future research. Potential areas of study could include identifying OCT biomarkers to predict significant ERMs, refining patient selection criteria for prophylactic ILM peeling and developing adjunctive therapies to modulate the inflammatory cascade driving membrane formation.

Until such advances materialize, the combination of vigilant surveillance, individualized surgical decision-making and timely intervention when indicated remains our best approach to optimizing outcomes for patients developing hyperacute ERMs after RRD repair.

REFERENCES

1. Bomdica PR, Shepherd EA, Gupta R, et al. Timing of epiretinal membrane surgery after uncomplicated retinal detachment repair. J Vitreoretin Dis 2025;24741264251337107
2. Sella R, Sternfeld A, Budnik I, et al. Epiretinal membrane following pars plana vitrectomy for rhegmatogenous retinal detachment repair. Int J Ophthalmol 2019;12:12:1872-1877
3. Akiyama K, Fujinami K, Watanabe K, et al. Retinal surface wrinkling as an indicator for internal limiting membrane peeling during vitrectomy for retinal detachment. Retina 2021;41:8:1618-1626
4. Matoba R, Kanzaki Y, Doi S, et al. Assessment of epiretinal membrane formation using en face optical coherence tomography after rhegmatogenous retinal detachment repair. Graefes Arch Clin Exp Ophthalmol 2021;259:9:2503-2512
5. Ishida Y, Iwama Y, Nakashima H, et al. Risk factors, onset, and progression of epiretinal membrane after 25-gauge pars plana vitrectomy for rhegmatogenous retinal detachment. Ophthalmol Retina 2020;4:3:284-288
6. Blackorby BL, Jeroudi AM, Blinder KJ, et al. Epiretinal membrane formation after treatment of retinal breaks: Cryoretinopexy versus laser retinopexy. Ophthalmol Retina 2019;3:12:1087-1090
7. Choi S, Goduni L, Wald KJ. Clinical outcomes of symptomatic horseshoe tears after laser retinopexy. J Vitreoretin Dis 2023;7:4:290-292
8. Szigiato AA, Antaki F, Javidi S, et al. Risk factors for epiretinal membrane formation and peeling following pars plana vitrectomy for primary rhegmatogenous retinal detachment, an OCT guided analysis. Int J Retina Vitr 2022;8:1:70
9. Hirakata T, Hiratsuka Y, Yamamoto S, et al. Risk factors for macular pucker after rhegmatogenous retinal detachment surgery. Sci Rep 2021;11:1:18276
10. Israilevich R, Salabati M, Mahmoudzadeh R, et al. Secondary epiretinal membrane after laser retinopexy for retinal tear or localized retinal detachment: Surgical outcomes and optical coherence tomography structural analysis. Retina 2022;42:1:38-45
11. Govetto A, Lalane RA, Sarraf D, et al. Insights into epiretinal membranes: Presence of ectopic inner foveal layers and a new optical coherence tomography staging scheme. Am J Ophthalmol 2017;175:99-113
12. Shepherd A, Chaturvedi V. Epiretinal membrane surgery within 1 year of retinal detachment repair: Clinical outcomes & anatomic characteristics. Invest Ophthalmol Vis Sci 2023;64:8:5249-5249
13. Council MD, Shah GK, Lee HC, et al. Visual outcomes and complications of epiretinal membrane removal secondary to rhegmatogenous retinal detachment. Ophthalmology 2005;112:7:1218-1221
14. Mylonas G, Sacu S, Deák G, et al. Macular edema following cataract surgery in eyes with previous 23-gauge vitrectomy and peeling of the internal limiting membrane. Am J Ophthalmol 2013;155:2:253-259.e2
15. Rush RB, Simunovic MP, Aragon AV, et al. Postoperative macular hole formation after vitrectomy with internal limiting membrane peeling for the treatment of epiretinal membrane. Retina 2014;34:5:890-896
16. Lamas-Francis D, Bande-Rodríguez M, Blanco-Teijeiro MJ. Primary ILM peeling during retinal detachment repair: A systematic review and meta-analysis. Sci Rep 2023;13:3586
17. Deltour JB, Grimbert P, Masse H, et al. Detrimental effects of active internal limiting membrane peeling during epiretinal membrane surgery: Microperimetric analysis. Retina 2017;37:3:544-552
18. Eckardt F, Klaas J, Siedlecki J, et al. Internal limiting membrane peeling in primary rhegmatogenous retinal detachment: Functional and morphologic results. Klin Monatsbl Augenheilkd 2025;242:2:153-159
19. Nam KY, Kim JY. Effect of internal limiting membrane peeling on the development of epiretinal membrane after pars plana vitrectomy for primary rhegmatogenous retinal detachment. Retina 2015;35:5:880-885

EYLEA HD® (aflibercept) Injection 8 mg, for intravitreal use AND EYLEA® (aflibercept) Injection 2 mg, for intravitreal use

BRIEF SUMMARY OF PRESCRIBING INFORMATION

4. CONTRAINDICATIONS

4.1 Ocular or Periocular Infections EYLEA HD and EYLEA are contraindicated in patients with ocular or periocular infections.

4.2 Active Intraocular Inflammation EYLEA HD and EYLEA are contraindicated in patients with active intraocular inflammation.

4.3 Hypersensitivity EYLEA HD and EYLEA are contraindicated in patients with known hypersensitivity to aflibercept or any of the excipients in EYLEA HD or EYLEA. Hypersensitivity reactions may manifest as rash, pruritus, urticaria, severe anaphylactic/anaphylactoid reactions, or severe intraocular inflammation.

5 WARNINGS AND PRECAUTIONS

5.1 Endophthalmitis, Retinal Detachments, and Retinal Vasculitis with or without Occlusion Intravitreal injections including those with aflibercept have been associated with endophthalmitis and retinal detachments [*see Adverse Reactions (6.1)*] and, more rarely, retinal vasculitis with or without occlusion [*see Adverse Reactions (6.2)*]. Proper aseptic injection technique must always be used when administering EYLEA HD or EYLEA. Patients and/or caregivers should be instructed to report any signs and/or symptoms suggestive of endophthalmitis, retinal detachment or retinal vasculitis without delay and should be managed appropriately [*see Dosage and Administration (2.7 EYLEA HD, 2.4 EYLEA) in the full Prescribing Information and Patient Counseling Information (17)*].

5.2 Increase in Intraocular Pressure Acute increases in intraocular pressure have been seen within 60 minutes of intravitreal injection, including with EYLEA HD and EYLEA [*see Adverse Reactions (6.1)*]. Sustained increases in intraocular pressure have also been reported after repeated intravitreal dosing with vascular endothelial growth factor (VEGF) inhibitors. Intraocular pressure and the perfusion of the optic nerve head should be monitored and managed appropriately [*see Dosage and Administration (2.7 EYLEA HD, 2.4 EYLEA) in the full Prescribing Information*].

5.3 EYLEA HD, 5.4 EYLEA Thromboembolic Events There is a potential risk of arterial thromboembolic events (ATEs) following intravitreal use of VEGF inhibitors, including EYLEA HD and EYLEA. ATEs are defined as nonfatal stroke, nonfatal myocardial infarction, or vascular death (including deaths of unknown cause).

- **EYLEA HD:** The incidence of reported thromboembolic events in the wet AMD study (PULSAR) from baseline through week 48 was 0.4% (3 out of 673) in the combined group of patients treated with EYLEA HD compared with 1.5% (5 out of 336) in patients treated with EYLEA 2 mg. The incidence of reported thromboembolic events in the DME study (PHOTON) from baseline to week 48 was 3.1% (15 out of 491) in the combined group of patients treated with EYLEA HD compared with 3.6% (6 out of 167) in patients treated with EYLEA 2 mg. The incidence of reported thromboembolic events in the RVO study (QUASAR) from baseline to week 36 was 0.5% (3 out of 591) in the combined group of patients treated with EYLEA HD compared with 1.7% (5 out of 301) in patients treated with EYLEA 2 mg.
- **EYLEA:** The incidence of reported thromboembolic events in wet AMD studies during the first year was 1.8% (32 out of 1824) in the combined group of patients treated with EYLEA compared with 1.5% (9 out of 595) in patients treated with ranibizumab; through 96 weeks, the incidence was 3.3% (60 out of 1824) in the EYLEA group compared with 3.2% (19 out of 595) in the ranibizumab group. The incidence in the DME studies from baseline to week 52 was 3.3% (19 out of 578) in the combined group of patients treated with EYLEA compared with 2.8% (8 out of 287) in the control group; from baseline to week 100, the incidence was 6.4% (37 out of 578) in the combined group of patients treated with EYLEA compared with 4.2% (12 out of 287) in the control group. There were no reported thromboembolic events in the patients treated with EYLEA in the first six months of the RVO studies.

6 ADVERSE REACTIONS The following potentially serious adverse reactions are described elsewhere in the labeling:

- Hypersensitivity [*see Contraindications (4.3)*]
- Endophthalmitis, Retinal Detachments, and Retinal Vasculitis with or without Occlusion [*see Warnings and Precautions (5.1)*]
- Increase in intraocular pressure [*see Warnings and Precautions (5.2)*]
- Thromboembolic events [*see Warnings and Precautions (5.3 for EYLEA HD, 5.4 for EYLEA)*]

6.1 Clinical Trials Experience Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in other clinical trials of the same or another drug and may not reflect the rates observed in practice.

- **EYLEA HD:** A total of 1755 patients were treated with EYLEA HD and 804 patients were treated with EYLEA 2 mg in three clinical studies. The most common adverse reactions reported in ≥3% of patients treated with EYLEA HD were cataract, conjunctival hemorrhage, corneal epithelium defect, intraocular pressure increased, ocular discomfort/eye pain/eye irritation, retinal hemorrhage, vision blurred, vitreous detachment, and vitreous floaters.
- **EYLEA:** A total of 2980 adult patients treated with EYLEA constituted the safety population in eight phase 3 studies. Among those, 2379 patients were treated with the recommended dose of 2 mg. Serious adverse reactions related to the injection procedure have occurred in <0.1% of intravitreal injections with EYLEA including endophthalmitis and retinal detachment. The most common adverse reactions (≥5%) reported in patients receiving EYLEA were conjunctival hemorrhage, eye pain, cataract, vitreous detachment, vitreous floaters, and intraocular pressure increased.

Macular Edema Following Retinal Vein Occlusion (RVO)

EYLEA HD: The data described below reflects 36 weeks exposure to EYLEA HD administered every 8 weeks (HDq8) after 3 or 5 initial monthly doses (HDq4), or EYLEA 2 mg administered every 4 weeks (2q4) in a controlled clinical study (QUASAR) [*see Clinical Studies (14.4) in the full Prescribing Information*].

EYLEA: The data described below reflect 6 months exposure to EYLEA with a monthly 2 mg dose in 218 patients following central retinal vein occlusion (CRVO) in 2 clinical studies (COPERNICUS and GALILEO) and 91 patients following branch retinal vein occlusion (BRVO) in one clinical study (VIBRANT) [*see Clinical Studies (14.2), (14.3) in the full Prescribing Information*].

Table 2: Most Common Adverse Reactions (≥1%) in RVO Studies

	RVO			CRVO		BRVO	
Adverse Reactions	**EYLEA HDq8 following 3 initial doses (HDq4) (n=293)**	**EYLEA HDq8 following 5 initial doses (HDq4) (n=298)**	**EYLEA 2q4 (n=301)**	**EYLEA (n=218)**	**Control (n=142)**	**EYLEA (n=91)**	**Control (n=92)**
Conjunctival hemorrhage[a]	3%	2%	2%	12%	11%	20%	4%
Eye pain	-	-	-	13%	5%	4%	5%
Intraocular pressure increased[a]	7%	6%	3%	8%	6%	2%	0%
Cataract[a]	2%	4%	3%	<1%	1%	5%	0%
Corneal epithelium defect[a]	2%	2%	2%	5%	4%	2%	0%
Ocular hyperemia	-	-	-	5%	3%	2%	2%
Vitreous floaters[a]	1%	1%	1%	5%	1%	1%	0%
Foreign body sensation in eyes	-	-	-	3%	5%	3%	0%
Vision blurred[a]	5%	3%	2%	1%	<1%	1%	1%
Vitreous detachment[a]	3%	3%	1%	3%	4%	2%	0%
Lacrimation increased	-	-	-	3%	4%	3%	0%
Ocular discomfort/eye pain/ eye irritation[a]	3%	3%	1%	-	-	-	-
Injection site pain	-	-	-	3%	1%	1%	0%
Dry eye[a]	2%	2%	2%	-	-	-	-
Intraocular inflammation[a]	1%	<1%	1%	1%	1%	0%	0%
Vitreous hemorrhage	1%	1%	0%	-	-	-	-
Eyelid edema	-	-	-	<1%	1%	1%	0%
Hypersensitivity[b]	1%	1%	1%	-	-	-	

Reported terms differ between the COPERNICUS, GALILEO, VIBRANT, and QUASAR studies, as indicated by dashes in the table.

[a]Represents grouping of related terms in QUASAR

[b]Represents reported non-ocular adverse events of hypersensitivity, rash, urticaria and pruritus

Adverse reactions reported in <1% of the patients treated with EYLEA HD in the RVO study were foreign body sensation in eyes (includes foreign body sensation in eyes and sensation of foreign body), ocular hyperaemia (includes conjunctival hyperemia, conjunctival irritation, ocular hyperemia), retinal hemorrhage, retinal pigment epithelial detachment (includes detachment of retinal pigment epithelium), retinal pigment epithelial tear/ epitheliopathy (includes retinal pigment epitheliopathy), and retinal tear.

Less common adverse reactions reported in <1% of the patients treated with EYLEA in the CRVO studies were corneal edema, retinal tear, hypersensitivity, and endophthalmitis.

6.2 Postmarketing Experience The following adverse reactions have been identified during postapproval use of aflibercept. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Eye disorders:

- Retinal vasculitis and occlusive retinal vasculitis related to intravitreal injection with aflibercept (reported at a rate of 0.6 and 0.2 per 1 million injections, respectively, based on postmarketing experience from November 2011 until November 2023).
- Scleritis.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy Risk Summary Adequate and well-controlled studies with EYLEA HD and EYLEA have not been conducted in pregnant women. Aflibercept produced adverse embryofetal effects in rabbits, including external, visceral, and skeletal malformations. A fetal No Observed Adverse Effect Level (NOAEL) was not identified. At the lowest dose shown to produce adverse embryofetal effects, systemic exposure (based on AUC for free aflibercept) was approximately 0.9-fold of the population pharmacokinetic estimated exposure in humans after an intravitreal dose of 8 mg for EYLEA HD and approximately 6 times higher than AUC values observed in humans after a single intravitreal treatment at the recommended clinical dose of 2 mg for EYLEA [*see Data*]. Animal reproduction studies are not always predictive of human response, and it is not known whether EYLEA HD or EYLEA can cause fetal harm when administered to a pregnant woman. Based on the anti-VEGF mechanism of action for aflibercept [*see Clinical Pharmacology (12.1) in the full Prescribing Information*], treatment with EYLEA HD or EYLEA may pose a risk to human embryofetal development. EYLEA HD and EYLEA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. The background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Data *Animal Data* In two embryofetal development studies, aflibercept produced adverse embryofetal effects when administered every three days during organogenesis to pregnant rabbits at intravenous doses ≥3 mg per kg, or every six days during organogenesis at subcutaneous doses ≥0.1 mg per kg.

Adverse embryofetal effects included increased incidences of postimplantation loss and fetal malformations, including anasarca, umbilical hernia, diaphragmatic hernia, gastroschisis, cleft palate, ectrodactyly, intestinal atresia, spina bifida, encephalomeningocele, heart and major vessel defects, and skeletal malformations (fused vertebrae, sternebrae, and ribs; supernumerary vertebral arches and ribs; and incomplete ossification). The maternal No Observed Adverse Effect Level (NOAEL) in these studies was 3 mg per kg. Aflibercept produced fetal malformations at all doses assessed in rabbits and the fetal NOAEL was not identified. At the lowest dose shown to produce adverse embryofetal effects in rabbits (0.1 mg per kg), systemic exposure (AUC) of free aflibercept was approximately 0.9-fold of the population pharmacokinetic estimated systemic exposure (AUC) in humans after an intravitreal dose of 8 mg for EYLEA HD and approximately 6 times higher than systemic exposure (AUC) observed in adult patients after a single intravitreal dose of 2 mg for EYLEA.

8.2 Lactation Risk Summary There is no information regarding the presence of aflibercept in human milk, the effects of the drug on the breastfed infant, or the effects of the drug on milk production/excretion. Because many drugs are excreted in human milk, and because the potential for absorption and harm to infant growth and development exists, EYLEA HD and EYLEA are not recommended during breastfeeding. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for EYLEA HD or EYLEA and any potential adverse effects on the breastfed child from EYLEA HD or EYLEA.

8.3 Females and Males of Reproductive Potential Contraception Females of reproductive potential are advised to use effective contraception prior to the initial dose, during treatment, and for at least 4 and 3 months after the last intravitreal injection of EYLEA HD or EYLEA, respectively.

Infertility There are no data regarding the effects of EYLEA HD or EYLEA on human fertility. Aflibercept adversely affected female and male reproductive systems in cynomolgus monkeys when administered by intravenous injection at a dose 91 times higher (based on AUC of free aflibercept) than the corresponding systemic level estimated based on population pharmacokinetic analysis in humans following an intravitreal dose of 8 mg for EYLEA HD and at a dose approximately 1500 times higher than the systemic level observed in adult patients with an intravitreal dose of 2 mg for EYLEA. A No Observed Adverse Effect Level (NOAEL) was not identified. These findings were reversible within 20 weeks after cessation of treatment [*see Nonclinical Toxicology (13.1) in the full Prescribing Information*].

8.4 Pediatric Use The safety and effectiveness of EYLEA HD in pediatric patients have not been established. The safety and effectiveness of EYLEA have been demonstrated in two clinical studies of pre-term infants with Retinopathy of Prematurity. These two studies randomized pre-term infants between initial treatment with EYLEA or laser. Efficacy of each treatment is supported by the demonstration of a clinical course which was better than would have been expected without treatment [*see Dosage and Administration (2.9), Adverse Reactions (6.1), Clinical Pharmacology (12.3) and Clinical Studies (14.6) in the full Prescribing Information for EYLEA*].

8.5 Geriatric Use In the clinical studies, approximately 66% (1156/1755) of the patients in the HD groups were 65 years of age or older and approximately 31% (543/1755) of the patients were 75 years of age or older.

No overall differences in safety or effectiveness of EYLEA HD have been observed.

10 OVERDOSAGE Overdosing with increased injection volume may increase intraocular pressure. Therefore, in case of overdosage, intraocular pressure should be monitored and if deemed necessary by the treating physician, adequate treatment should be initiated.

17 PATIENT COUNSELING INFORMATION In the days following EYLEA HD or EYLEA administration, patients are at risk of developing endophthalmitis, retinal detachment, or retinal vasculitis with or without occlusion. If the eye becomes red, sensitive to light, painful, or develops a change in vision, advise patients and/or caregivers to seek immediate care from an ophthalmologist [*see Warning and Precautions (5.1)*]. Patients may experience temporary visual disturbances after an intravitreal injection with EYLEA HD or EYLEA and the associated eye examinations [*see Adverse Reactions (6.1)*]. Advise patients not to drive or use machinery until visual function has recovered sufficiently.

REGENERON®

Manufactured by: **Regeneron Pharmaceuticals, Inc.**
777 Old Saw Mill River Road, Tarrytown, NY 10591-6707

 US.EHD.25.08.0012 12/2025

STRENGTH THAT ENDURES

AS SHOWN BY SIMILAR VISION OUTCOMES WITH EYLEA HD VS EYLEA® (aflibercept) Injection 2 MG IN PATIENTS WITH MEfRVO (WEEK 36)[1]*†

EYLEA HD®
(aflibercept) Injection 8 mg

NOW APPROVED FOR MEfRVO[1]

DISCOVER MORE ABOUT EYLEA HD

DELIVERED RAPID AND DURABLE VISION GAINS[1,2*†]	PROVIDED ANATOMIC IMPROVEMENTS[2‡]	FEATURES DOSING FLEXIBILITY IN APPROPRIATE PATIENTS[1]	DEMONSTRATED SAFETY PROFILE CONSISTENT WITH EYLEA 2 mg[1,3]

*Mean change in BCVA (ETDRS letters) from baseline at Week 36: FAS at baseline. FAS; observed values (censoring data post ICE) at Week 36: EYLEA HD Q8W/3 +17.0 letters (n=260), EYLEA HD Q8W/5 +19.1 letters (n=248), EYLEA 2 mg Q4W +17.8 letters (n=264) in QUASAR. EYLEA HD groups received treatment Q8W after 3 or 5 monthly injections, while the EYLEA 2 mg group received treatment Q4W.[1,2]

†Some patients saw vision improvement at Week 12 (exploratory endpoint): FAS at baseline. FAS; observed values at Week 12: EYLEA HD Q8W/3 +14.7 letters (n=283), EYLEA HD Q8W/5 +16.0 (n=285), EYLEA 2 mg Q4W +15.5 (n=289).[2]

‡Reductions in CRT were achieved through Week 36 in QUASAR in patients with MEfRVO. Mean change in CRT at Week 36 was a prespecified additional secondary endpoint. **Outcomes are descriptive only.**[2,4]

QUASAR Study Design:
Randomized, multicenter, double-masked, Phase 3 clinical study in which treatment-naïve patients with MEfRVO (N=892 [425 with CRVO/HRVO, 467 with BRVO]; age range: 23-95 years, with a mean of 65.9 years) were randomized in a 1:1:1 ratio to receive: (1) EYLEA HD Q8W (n=293), following 3 initial monthly doses (Q8W/3); (2) EYLEA HD Q8W (n=298), following 5 initial monthly doses (Q8W/5); or (3) EYLEA 2 mg Q4W (n=301). Dosing intervals could be shortened or extended by 4-week increments based on protocol-defined visual and anatomic criteria, with a minimum interval of Q4W for all patients. Intervals could be shortened beginning at Week 16 for the EYLEA HD Q8W/3 group, at Week 24 for the EYLEA HD Q8W/5 group and, if previously extended, at Week 40 for the EYLEA 2 mg Q4W group. Intervals could be extended beginning at Week 32 for the EYLEA HD Q8W/3 and EYLEA 2 mg Q4W groups and at Week 40 for the EYLEA HD Q8W/5 group. The primary endpoint was the mean change from baseline in BCVA at Week 36 as measured by the ETDRS letter score.[1,4]

INDICATIONS

EYLEA HD® (aflibercept) Injection 8 mg and EYLEA® (aflibercept) Injection 2 mg are indicated for the treatment of patients with Macular Edema following Retinal Vein Occlusion (RVO).

IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS

- EYLEA HD and EYLEA are contraindicated in patients with ocular or periocular infections, active intraocular inflammation, or known hypersensitivity to aflibercept or any of the excipients in EYLEA HD or EYLEA.

WARNINGS AND PRECAUTIONS

- Intravitreal injections, including those with aflibercept, have been associated with endophthalmitis and retinal detachments and, more rarely, retinal vasculitis with or without occlusion. Proper aseptic injection technique must always be used when administering EYLEA HD or EYLEA. Patients and/or caregivers should be instructed to report any signs and/or symptoms suggestive of endophthalmitis, retinal detachment, or retinal vasculitis without delay and should be managed appropriately.
- Acute increases in intraocular pressure (IOP) have been seen within 60 minutes of intravitreal injection, including with EYLEA HD and EYLEA. Sustained increases in IOP have also been reported after repeated intravitreal dosing with VEGF inhibitors. IOP and the perfusion of the optic nerve head should be monitored and managed appropriately.
- There is a potential risk of arterial thromboembolic events (ATEs) following intravitreal use of VEGF inhibitors, including EYLEA HD and EYLEA. ATEs are defined as nonfatal stroke, nonfatal myocardial infarction, or vascular death (including deaths of unknown cause).
  - EYLEA HD: The incidence of reported ATEs in the RVO study from baseline to week 36 was 0.5% (3 out of 591) in the combined group of patients treated with EYLEA HD compared with 1.7% (5 out of 301) in patients treated with EYLEA 2 mg.
  - EYLEA: There were no reported thromboembolic events in the patients treated with EYLEA in the first six months of the RVO studies.

ADVERSE REACTIONS

- **EYLEA HD:** The most common adverse reactions (≥3%) reported in patients receiving EYLEA HD were cataract, conjunctival hemorrhage, corneal epithelium defect, intraocular pressure increased, ocular discomfort/eye pain/eye irritation, retinal hemorrhage, vision blurred, vitreous detachment, and vitreous floaters.
- **EYLEA:** Serious adverse reactions related to the injection procedure have occurred in <0.1% of intravitreal injections with EYLEA including endophthalmitis and retinal detachment. The most common adverse reactions (≥5%) reported in patients receiving EYLEA were conjunctival hemorrhage, eye pain, cataract, vitreous detachment, vitreous floaters, and intraocular pressure increased.
- Patients may experience temporary visual disturbances after an intravitreal injection with EYLEA HD or EYLEA and the associated eye examinations. Advise patients not to drive or use machinery until visual function has recovered sufficiently.

Please see brief summary of full Prescribing Information for EYLEA HD and EYLEA on the following page.

BCVA, best-corrected visual acuity; BRVO, branch retinal vein occlusion; CRT, central retinal thickness; CRVO, central retinal vein occlusion; ETDRS-DRSS, Early Treatment Diabetic Retinopathy Study–Diabetic Retinopathy Severity Scale; FAS, full analysis set; HRVO, hemiretinal vein occlusion; ICE, intercurrent event; Q4W, every 4 weeks; Q8W, every 8 weeks; Q8W/3, every 8 weeks after 3 initial monthly injections; Q8W/5, every 8 weeks after 5 initial monthly injections.

References: 1. EYLEA HD full U.S. Prescribing Information. Regeneron Pharmaceuticals, Inc. November 2025. **2.** Data on file. Regeneron Pharmaceuticals, Inc. **3.** EYLEA full U.S. Prescribing Information. Regeneron Pharmaceuticals, Inc. October 2024. **4.** Gale R; QUASAR Group. Aflibercept 8 mg in retinal vein occlusion: primary endpoint results from the QUASAR trial. Presented at: Angiogenesis Meeting 2025; February 8, 2025; virtual.

REGENERON®

12/2025
US.EHD.25.07.0079